DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
Silver Spring MD 20993-0002

To:	Administrative File: STN 125614/0, SHINGRIX®, Zoster Vaccine Recombinant, Adjuvanted
From:	CDR Jeremy L. Wally, PhD, CMC/Facilities and Equipment Reviewer, CBER/OCBQ/DMPQ/MRB2
Through:	John A. Eltermann, Division Director, CBER/OCBQ/DMPQ CDR Qiao Bobo, Branch Chief, CBER/OCBQ/DMPQ/MRB2
CC:	Anthony Lorenzo, Team Leader, CBER/OCBQ/DMPQ/MRB2 Carmen Collazo-Custodio, Chair, CBER/OVRR/DVRPA/CMC3 Shuang Tang, Product Reviewer, CBER/OVRR/DVP/LDV Marina Zaitseva, Product Reviewer, CBER/OVRR/DVP/LR Ramachanda Naik, RPM, CBER/OVRR/DVRPA/CMC3 Michael Smith, RPM, CBER/OVRR/DVRPA/CMC3
Subject:	Original Biologics License Application
Indication/ Drug Info:	Prevention of herpes zoster (shingles) in adults aged 50 years and older.
Applicant:	GlaxoSmithKline Biologicals, S. A.
License Number:	1617
Facility Site:	(b) (4) Rixensart, Belgium (FEI 3002875226) (b) (4)
Action Due Date:	October 21, 2017
Recommendation:	Approval

REVIEW SUMMARY

This Biologics License Application (BLA) for SHINGRIX was submitted on October 21, 2016, by GlaxoSmithKline Biologicals, S. A. (GSK). SHINGRIX is a herpes zoster (HZ) vaccine consisting of a lyophilized recombinant varicella zoster virus (VZV) glycoprotein E (gE) as the antigen (gE Antigen) combined with liquid $AS01_B$ Adjuvant. CMC information for the Drug

Substance (b) (4) Liquid Drug Product ($AS01_B$ Adjuvant) and Lyophilized Drug Product (gE Antigen), and for the manufacturing facilities, Buildings (b) (4) were provided in the BLA and amendments. Pre-license inspections of applicable manufacturing facilities were waived for this BLA as described in a separate inspection waiver memo. In addition, the BLA includes three Comparability Protocols (CPs) covering the following items:

(b) (4)

PRODUCT SUMMARY
SHINGRIX consists of lyophilized gE Antigen and liquid $AS01_B$ Adjuvant. The gE Antigen is a purified recombinant protein produced in Chinese Hamster Ovary (b) (4) (CHO(b) (4)) cells that is supplied in a lyophilized form in single-dose vials (50 µg/dose). The $AS01_B$ Adjuvant contains 50 µg of QS-21 (*Quillaja saponaria* Molina, fraction 21; manufactured by (b) (4) and MPL (3-O-desacyl-4'-monophosphoryl lipid A; manufactured by GSK Biologicals (b) (4)) combined with liposomes composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol in a Phosphate-Buffered Saline (PBS) solution that is supplied in separate single-dose vials (0.5 mL/dose). The contents of the $AS01_B$ Adjuvant vial is used to reconstitute the contents of the gE Antigen vial immediately prior to injection. SHINGRIX is to be administered in two doses (0.5 mL each) by intramuscular injection at Month 0 and between 2 and 6 months later, respectively.

Based upon review of the in-scope information provided in the original submission and amendments of December 21, 2016 (STN 125614/0/5), March 30, 2017 (STN 125614/0/15), May 5, 2017 (STN 125614/0/19), June 30, 2017 (STN 125614/0/27), August 8, 2017 (STN 125614/0/33), August 14, 2017 (STN 125614/0/37), August 24, 2017 (STN 125614/0/38), and October 16, 2017 (STN 125614/0/54) for this BLA, approval of this BLA is recommended.

CONTENTS OF SUBMISSIONS REVIEWED
This is an electronic submission in eCTD format. The original submission (DCC Login ID#641859) contains the following documentation that was reviewed:

- **Section 1:** Cover Letter, Form FDA 356h, CMC Meeting Documentation, and Request for Categorical Exclusion from Environmental Assessment
- **Section 2:** Introductory Summary Documents regarding the Drug Substance, Drug Product and Manufacturing Facilities
- **Section 3.2.S:** In-Scope CMC information on the Drug Substance (b) (4)
- **Section 3.2.P:** In-Scope CMC information on the Liquid Drug Product ($AS01_B$ Adjuvant) and Lyophilized Drug Product (gE Antigen)
- **Section 3.2.A:** Facility information on the Drug Substance, Liquid Drug Product ($AS01_B$ Adjuvant) and Lyophilized Drug Product (gE Antigen) Manufacturing Facilities

- **Section 3.2.R:** Blank and Executed Batch Records for the Drug Substance, Liquid Drug Product ($AS01_B$ Adjuvant) and Lyophilized Drug Product (gE Antigen), three CPs, and Cross-Reference Letters for the Master Files for the (b) (4) Stoppers, and for MPL (b) (4) and QS-21 (b) (4)

The amendment of December 21, 2016 (STN 125614/0/5; DCC Login ID#652752) contains the following documentation that was reviewed:

- **Section 1:** Cover Letter and Form FDA 356h
- **Section 3.2.P.3.5:** Additional information regarding decontamination of the (b) (4) used for the gE Antigen and data to support aseptic processing in reference to agreements made during the Type B Pre-BLA meeting held under INDs 13857 and 13879 on July 7, 2016

The amendment of March 30, 2017 (STN 125614/0/15; DCC Login ID#652752) contains the following documentation that was reviewed:

- **Section 1:** Cover Letter, Form FDA 356h and follow-up on GSK's intention to submit supporting data regarding use of more precise equipment for measuring (b) (4) during decontamination of the (b) (4) used for the gE Antigen stated during the Type B Pre-BLA meeting held under INDs 13857 and 13879 on July 7, 2016

The amendment of May 5, 2017 (STN 125614/0/19; DCC Login ID#676377) contains the following documentation that was reviewed:

- **Section 1:** Cover Letter, Form FDA 356h and the response to comment #1 regarding validation of sterilizing filters used for the $AS01_B$ Adjuvant and intermediates in the Information Request of April 18, 2017 (requested by the assigned product office reviewer)

The amendment of June 30, 2017 (STN 125614/0/27; DCC Login ID#687571) contains the following documentation that was reviewed:

- **Section 1:** Cover Letter, Form FDA 356h and responses to the comments in the Information Request of June 5, 2017

The amendment of August 8, 2017 (STN 125614/0/33; DCC Login ID#693860) contains the following documentation that was reviewed:

- **Section 1:** Cover Letter, Form FDA 356h and a response to the comments in the Information Request of July 24, 2017
- **Section 3.2.A.1:** Validations of test organism viability

The amendment of August 14, 2017 (STN 125614/0/37; DCC Login ID#695163) contains the following documentation that was reviewed:

- **Section 1:** Cover Letter, Form FDA 356h and document summarizes corrections and clarifications made to the Sections 2.3, 3.2.S, 3.2.P and 3.2.A
- **Section 2.3:** Revised summary documents regarding the Liquid Drug Product ($AS01_B$ Adjuvant) and Lyophilized Drug Product (gE Antigen)
- **Section 3.2.S:** Revised CMC information regarding the Drug Substance (b) (4))
- **Section 3.2.P:** Revised CMC information regarding the Liquid Drug Product ($AS01_B$ Adjuvant) and Lyophilized Drug Product (gE Antigen)
- **Section 3.2.A:** No in-scope changes were made to this Section

The amendment of August 24, 2017 (STN 125614/0/38; DCC Login ID#696669) contains the following documentation that was reviewed:

- **Section 1:** Cover Letter, Form FDA 356h and a response to comment #6 in the Information Request of June 5, 2017

The amendment of October 16, 2017 (STN 125614/0/54; DCC Login ID#706241) contains the following documentation that was reviewed:

- **Section 1:** Cover Letter, Form FDA 356h and a response to the comments in the Information Request of October 11, 2017

REVIEW

Review Process

The original submission for this BLA was submitted on October 21, 2016. Subsequent to submission of the BLA, two additional amendments were submitted on December 21, 2016 (STN 125614/0/5) and March 30, 2017 (STN 125614/0/15) in follow-up to discussions that occurred during the Type B Pre-BLA meeting of July 7, 2016 held under INDs 13857 and 13879. These amendments are respectively reviewed below under *Review of Amendment 5* and *Review of Amendment 15*.

In addition, an Information Request containing four comments from the assigned product office reviewer was emailed to GSK on April 17, 2017. GSK responded to this Information Request in an amendment of May 5, 2017 (STN 125614/0/19). The in-scope portion of the response (comment #1 regarding validation of sterilizing filters used for the $AS01_B$ Adjuvant and intermediates) to this Information Request is reviewed below under *Review of Amendment 19*. References to this comment in this Information Request are provided throughout this memo.

Based upon review of the original submission and amendments 5 and 15, an Information Request containing 27 comments was emailed to GSK on June 5, 2017. GSK responded to this Information Request in an amendment of June 30, 2017 (STN 125614/0/27), except for comment #6 for which a response was provided in an amendment of August 24, 2017 (STN 125614/0/38). The responses to this Information Request are reviewed below under *Review of Amendment 27* and *Review of Amendment 38*. In addition, based upon review of amendment 19 (response to comment #1 only) and amendment 27, a second Information Request containing three comments was emailed to GSK on July 24, 2017. GSK also responded to this Information Request in

amendment of August 8, 2017 (STN 125614/0/33). The responses to this Information Request are reviewed below under *Review of Amendment 33*. References to the comments in these Information Requests are provided throughout this memo.

An additional amendment was submitted on August 14, 2017 (STN 125614/0/37) to update the BLA in order to make corrections and clarifications identified by GSK. The in-scope changes made based upon the information provided in this amendment are noted throughout this memo. Finally, based upon additional review of the original submission and amendment 27, an Information Request containing 2 comments was emailed to GSK on October 11, 2017. GSK responded to this Information Request in amendment of October 16, 2017 (STN 125614/0/54). The responses to this Information Request are reviewed below under *Review of Amendment 54*. References to the comments in this Information Request are provided throughout this memo.

Environmental Assessment

GSK requests a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR 25.31(c) as the biologic product to be marketed under this BLA occurs naturally in the environment and does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. In addition, GSK states that, to the best of their knowledge, no extraordinary circumstances exist that would require an environmental assessment (under 21 CFR part 25.21).

Reviewer's Comments: *The request for categorical exclusion from environmental assessment for SHINGRIX is accepted.*

Drug Substance (b) (4)

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

(b) (4)

Liquid Drug Product ($AS01_B$ Adjuvant)

$AS01_B$ Adjuvant Description

The $AS01_B$ Adjuvant is an opalescent, colorless to pale brownish liquid suspension, provided in a 3 mL glass vial closed with a rubber stopper and (b) (4) cap. The $AS01_B$ Adjuvant is used to reconstitute the lyophilized Drug Product (see below under *gE Antigen*) before administration. The $AS01_B$ Adjuvant does not contain any Drug Substance. The $AS01_B$ Adjuvant (0.5 mL dose/vial with an (b) (4) is composed of:

- 50 µg/0.5 mL QS-21 (a triterpene glycoside purified from the (b) (4) of *Quillaja saponaria* Molina)
- 50 µg/0.50 mL MPL
- Liposomes composed of 1 mg/0.5 mL DOPC and 250 µg/0.5 mL cholesterol
- PBS solution (b) (4) disodium phosphate anhydrous, (b) (4) potassium dihydrogen phosphate, (b) (4) sodium chloride, and Water For Injection (WFI)]

$AS01_B$ Adjuvant Manufacturers

The $AS01_B$ Adjuvant is manufactured at the following sites:

Manufacturer	Responsibilities
GlaxoSmithKline Biologicals S.A. (b) (4)	• Production of intermediates • Formulation and filling • Labelling and packaging • Quality Control release testing
(b) (4)	• Labelling and packaging operations • Quality Control release testing • Quality Assurance release
GlaxoSmithKline Biologicals S.A. Rue de l'Institut 89 1330 Rixensart, Belgium FEI 3002875226	• Quality Assurance release

*Added to the address in the amendment of August 14, 2017 (STN 125614/0/37).

Information regarding the manufacturing site for the $AS01_B$ Adjuvant is provided below under *Manufacturing Facility Descriptions*.

$AS01_B$ Adjuvant Manufacturing Process Description

The manufacturing process for the $AS01_B$ Adjuvant is comprised of the following steps (performed in Buildings (b) (4) in existing rooms used to manufacture other US-licensed products):

(b) (4)

Step Description	Processes Performed	Room(s)
[redacted]	(b) (4) [redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Formulation of the $AS01_B$ Adjuvant (b) (4) [redacted]	(b) (4) [redacted]	[redacted]

Step Description	Processes Performed	Room(s)
[redacted]	[redacted]	[redacted]
Visual Inspection of the $AS01_B$ Adjuvant FC Building (b) (4)	• (b) (4) . • Storage of the accepted vials at 2-8°C at the warehouse. • (b) (4)	(b) (4)
Labeling and Packaging of the $AS01_B$ Adjuvant FC Building (b) (4) Building (b) (4)	• Automatic labeling of the vials on a labeling machine performed in Building (b) (4) . • Manually packaging of the vials into labeled cardboard boxes (packaging (b) (4) palletization and storage at 2-8°C until release.	(b) (4)

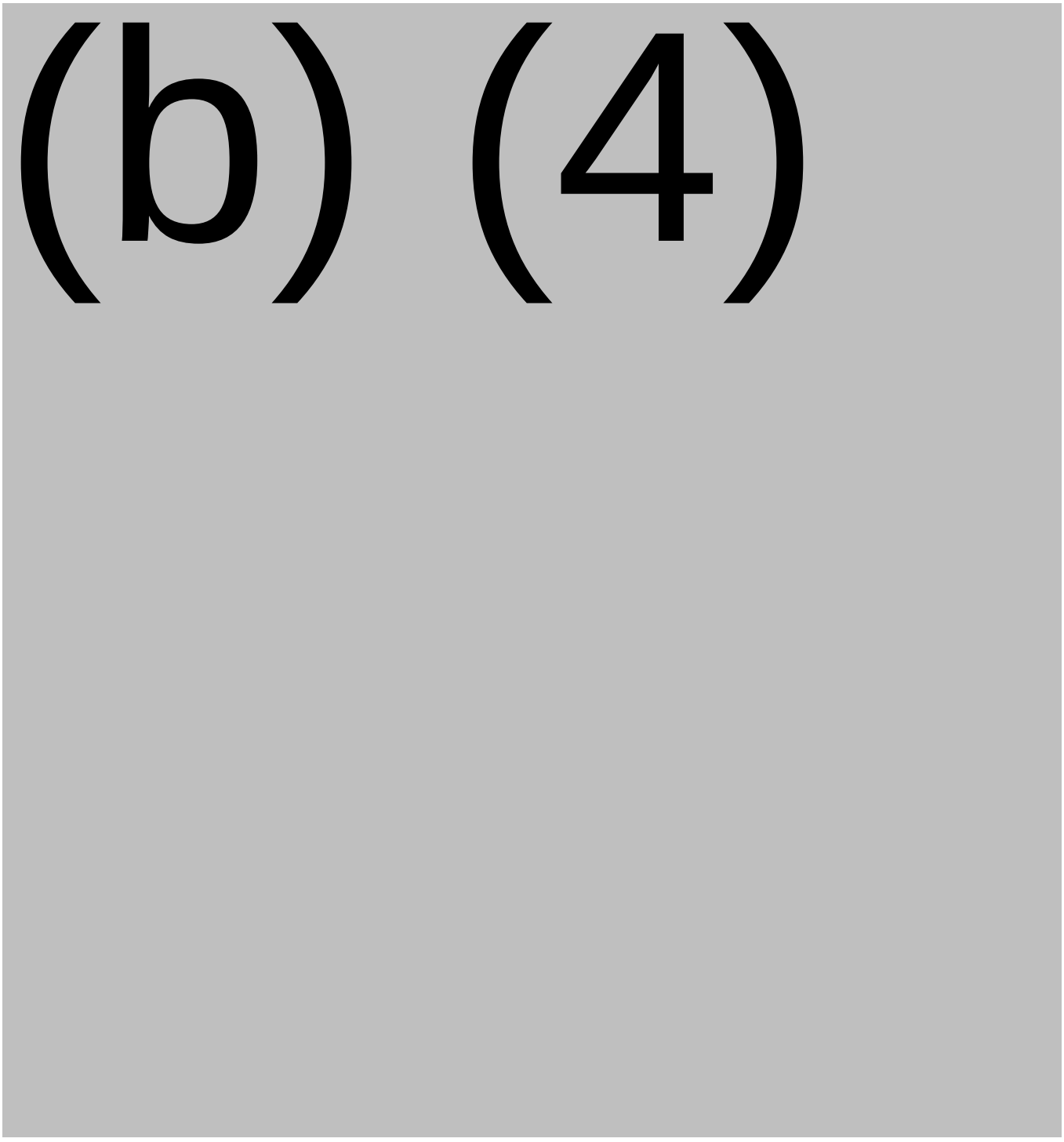
$AS01_B$ Adjuvant Control Strategy

The following in-scope CQAs and CPAs for the $AS01_B$ Adjuvant manufacturing process were identified during process design:

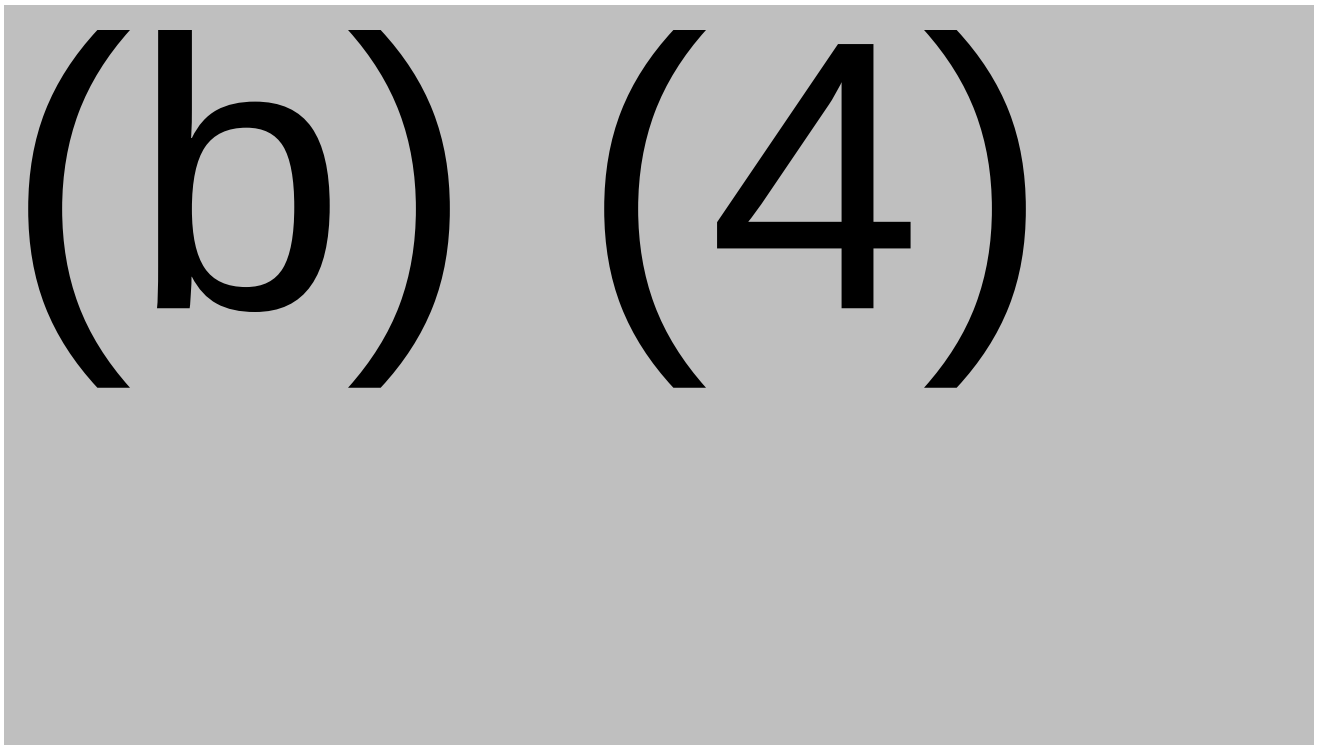
- **MPL** (b) (4)
- **QS-21** (b) (4)
- **AS01$_B$ Adjuvant** (b) (4)
- **AS01$_B$ Adjuvant FC Filling:** endotoxin, sterility, appearance, volume and rejection rate

Based upon these CQAs and CPPs, and a risk assessment, the following in-scope CPPs for the AS01$_B$ Adjuvant manufacturing process were identified during process design:

(b) (4)



Based upon the identification of these in-scope CPPs, the following control strategies (testing) were defined for the in-scope CQAs and CPAs for the $AS01_B$ Adjuvant manufacturing process:



$AS01_B$ Adjuvant Raw Materials

The following raw materials are used to manufacture the $AS01_B$ Adjuvant: MPL, QS-21, DOPC and cholesterol (and excipients disodium phosphate anhydrous, potassium dihydrogen phosphate, NaCl and WFI). All of these raw materials are covered under the (b) (4) except for QS-21 and DOPC. In addition, GSK considers QS-21, DOPC and cholesterol to be novel excipients as they have not previously been used in a Drug Product for intramuscular use (to their knowledge). MPL is currently included in CERVARIX (for intramuscular use). WFI is manufactured by GSK in house. With the exception of the (b) (4) used during the production process for MPL, no materials from human or animal origin are used in the manufacture of the $AS01_B$ Adjuvant. The (b) (4) . The raw materials are described in more detail as follows:

MPL

MPL is a (b) (4) (b) (4)

QS-21

QS-21 is a saponin purified from the (b) (4) of the South American tree *Quillaja saponaria Molina*. QS-21 is purchased from a commercial supplier (b) (4) . Before use, QS-21 is not tested for any in-scope parameters (b) (4)).

DOPC
DOPC is a semi-synthetic phospholipid produced from (b) (4)

Cholesterol
Cholesterol is a (b) (4)

$AS01_B$ Adjuvant (b) (4)

Reviewer's Comments: (b) (4)

$AS01_B$ Adjuvant Specifications
The specifications for the $AS01_B$ Adjuvant and its intermediates are shown in the following table:

(b) (4)

Component	Test	Specification
$AS01_B$ Adjuvant FC	Appearance	Opalescent, colorless to pale brownish liquid; (b) (4)
	Volume	(b) (4)
	Sterility (b) (4)	(b) (4)

Reviewer's Comments: *The specification for the $AS01_B$ Adjuvant FC does not include a specification for endotoxin. However, a specification for pyrogenicity (b) (4)) was included for the (b) (4) lots but was removed for the (b) (4) lots. Evaluation of the acceptability of this testing plan, and the taking of any actions to address any issues, is deferred to the assigned product reviewer.*

$AS01_B$ Adjuvant Process Development

The changes to the manufacturing process of the $AS01_B$ Adjuvant and its intermediates during development are shown in the following table (changes in bold). (b) (4) batches were industrialization batches used for clinical studies while (b) (4) batches were PPQ batches and (b) (4) batches were commercial batches.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

$AS01_B$ Adjuvant FC Storage	2-8 C glass vials

(b) (4)

The following notable changes to the manufacturing process were made for the commercial batches (b) (4)

(b) (4)

Reviewer's Comments: *Evaluation of the impact of these changes (and the other changes described in the above table) was performed during the manufacture of the PPQ batches and is described below under* $AS01_B$ Adjuvant Process Validation.

The genealogy of the $AS01_B$ Adjuvant FC developmental lots manufactured in support of this BLA is shown in the following table.

(b) (4)

(b) (4)

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

(b) (4)

Lyophilized Drug Product (gE Antigen)

gE Antigen Description

The gE Antigen is a white powder containing 50 µg of gE, 20 mg sucrose, 0.08 mg Polysorbate 80, 0.160 mg sodium dihydrogen phosphate dihydrate and 0.116 mg dipotassium phosphatelyophilized from a fill volume of 0.5 mL in a single-dose 3 mL glass vial closed with a rubber stopper and (b) (4) cap. (b) (4)

The gE Antigen is reconstituted using the $AS01_B$ Adjuvant before use. No preservative is included in the gE Antigen.

gE Antigen Manufacturers
The gE Antigen is manufactured at the following facilities:

Manufacturer	Responsibilities
GlaxoSmithKline Biologicals SA (b) (4)	• Formulation, filling and lyophilization • Labelling and packaging • Quality Control testing
(b) (4)	• Labelling and packaging • Quality Control testing • Quality Assurance release
GlaxoSmithKline Biologicals S.A. Rue de l'Institut 89 1330 Rixensart, Belgium FEI 3002875226	• Quality Assurance release

*Added to the address in the amendment of August 14, 2017 (STN 125614/0/37).

Information regarding the manufacturing site for the gE Antigen is provided below under *Manufacturing Facility Descriptions*.

gE Antigen Manufacturing Process Description
The manufacturing process for the gE Antigen is comprised of the following steps (performed in Buildings (b) (4) in existing rooms used to manufacture other US-licensed products):

Step Description	Processes Performed	Room(s)
(b) (4)		

Step Description	Processes Performed	Room(s)
(b) (4)		
Visual Inspection of the gE Antigen FC Building (b) (4)	• MVI in Building (b) (4) to detect empty vials, particles and non-conformity of the container closure system, and lyophilization defects. • Storage of the vials at 2-8°C at the warehouse. • (b) (4) .	(b) (4)

Step Description	Processes Performed	Room(s)
Labeling and Packaging of the gE Antigen FC Building (b) (4) Building (b) (4)	• Automatic labeling of the vials on a labeling machine performed in Building (b) (4) • Manually packaging of the vials into labeled cardboard boxes (packaging (b) (4) palletization and storage at 2-8°C until release.	(b) (4)

The lyophilization cycle (target process parameters and acceptable ranges for the different steps) for the gE Antigen is shown in the following figure.

(b) (4)

(b) (4)

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(b) (4)

gE Antigen Process Development

The first gE Antigen FC lot (DVZV001A21; used for the Phase 1/2 clinical trial) was a liquid formulation filled in a single-dose vial at a volume of (b) (4) that was mixed with the $AS01_B$

Adjuvant before use. A lyophilized formulation was developed and used for the subsequent clinical trials and the commercial lots. The composition of the gE Antigen lots varies depending upon the gE Antigen (b) (4) manufacturing process used. For the (b) (4) lot (DVZV001A21), only (b) (4) sodium dihydrogen phosphate dihydrate was included with the gE. For the (b) (4) lot (DVZVA001A), 20 mg sucrose, (b) (4) sodium dihydrogen phosphate dihydrate and (b) (4) dipotassium phosphate was included with the gE. All Process (b) (4) lots (DVZVA003A through DVZVA021A and the commercial lots) contain the formulation described above under *gE Antigen Description*.

Additional information on the differences between (b) (4) are provided in the following table. The genealogy of the gE Antigen lots manufactured in support of this BLA are provided above under *gE Antigen Purified Bulk Process Development*.

(b) (4)

gE Antigen Control Strategy
The following in-scope CQAs and CPAs for the gE Antigen manufacturing process were identified during process design: (b) (4)

Based upon these CQAs and CPPs, and a risk assessment, the in-scope CPPs for the gE Antigen manufacturing process shown in the following table were identified during process design.

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

(b) (4)

Reviewer's Comments: *No limits for the fill volume of the gE Antigen FC for commercial manufacturing were specified in the BLA. GSK was therefore asked in an* ***Information Request of June 5, 2017 (comment #5)*** *to set limits for this testing. The response is reviewed below under* Review of Amendment 27.

Based upon the identification of these in-scope CPPs, the following control strategies (testing) were defined for the in-scope CQAs and CPAs for the gE Antigen manufacturing process:

(b) (4)

gE Antigen Raw Materials
The excipients used to manufacture gE Antigen are sucrose, Polysorbate 80, sodium dihydrogen phosphate dihydrate and dipotassium phosphate. These excipients are purchased from commercial supplier and comply with the (b) (4) . No excipients of human or animal origin are used in the manufacture of the gE Antigen.

gE Antigen In-Process Testing
The gE Antigen FB is in-scope in-process tested for (b) (4) as a monitoring test (for investigations and trending only).

gE Antigen Specifications
gE Antigen FB Specifications
The specification for the gE Antigen FB consists of in-scope testing for (b) (4)

gE Antigen FC Specifications
The specification for the gE Antigen FC includes in-scope testing for appearance (AC white cake or powder; clear to opalescent, colorless liquid after reconstitution with water for injection; (b) (4) endotoxin (b) (4) and sterility (b) (4)

The gE Antigen FC is also in-scope tested for CCIT (b) (4)) after capping of lyophilized and stoppered vials as a monitoring test (for investigations and trending only) and

visually inspected for particulates after reconstitution (AC essentially free from extraneous visible particulates after reconstitution with WFI) as a quality-decision test (used to demonstrate that the process is in control; batches are discarded if they fail to meet the acceptance criteria).

gE Antigen Final Product Specifications
The specification for the Final Product (labeled and packaged gE/$AS01_B$) does not include any in-scope testing (only identity gE on the lyophilized gE Antigen and identity cholesterol on the liquid $AS01_B$ Adjuvant).

gE Antigen Process Validation
The genealogy of the gE Antigen FC lots manufactured in support of this BLA is shown above under *gE Antigen* (b) (4) . (b) (4) gE Antigen PPQ FC lots were produced in Building (b) (4) (commercial facility) from (b) (4) gE Antigen FB batches were produced in Building (b) (4) (commercial facility) from (b) (4) gE Antigen (b) (4) batches as shown in the following table in order to demonstrate manufacturing consistency as well as comparability to the Phase 3 clinical batches. The gE Antigen PPQ FC lots were reconstituted with $AS01_B$ Adjuvant PPQ lots resulting in (b) (4) different gE/$AS01_B$ Reconstituted Vaccine PPQ lots also shown in the table.

(b) (4)

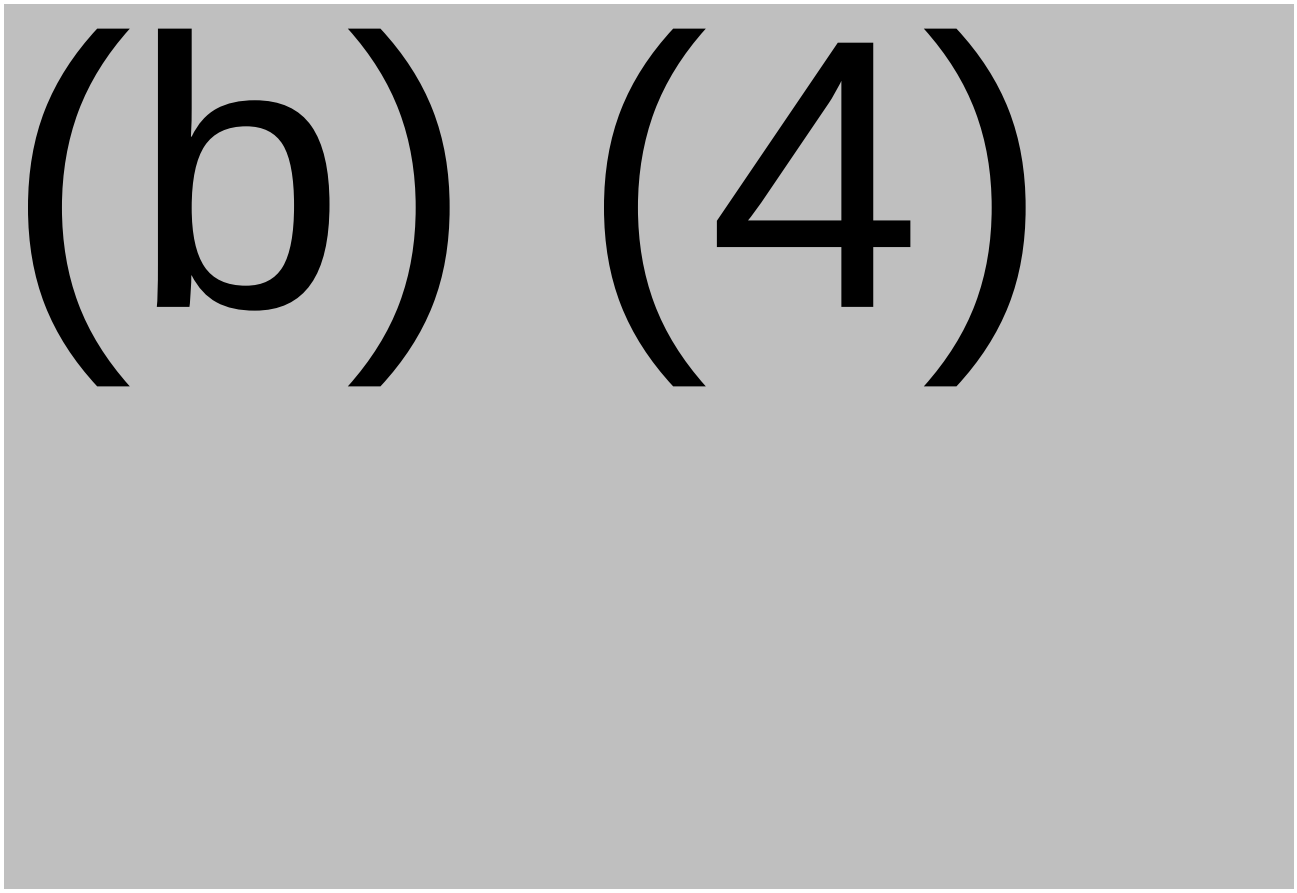
In addition, (b) (4) gE Antigen FC lots (b) (4) ranging from (b) (4) vails per lot were manufactured during the same campaign as the PPQ lots in order to complete the validation of the secondary process (formulation, filling and lyophilization) but were not considered by GSK to be PPQ lots.

The results for the (b) (4) gE Antigen FB PPQ batches were compared to each other. They were also compared to the (b) (4) Phase 3 clinical gE Antigen FB batches (see above under *gE Antigen* (b) (4) *Process Development*; however, no in-scope results were provided for comparison). The PPQ lot comparison is shown in the following table (only in-scope results are shown). The acceptance criteria for the release testing for sterility are provided above under *gE Antigen Specifications*.

(b) (4)

*Release testing

The results for the (b) (4) gE Antigen FC PPQ lots were compared to each other. They were also compared to the (b) (4) Phase 3 clinical gE Antigen FC lots (see above under *gE Antigen* (b) (4) *Process Development*; however, no in-scope results were provided for comparison). The PPQ lot comparison is shown in the following table (only in-scope results are shown). The acceptance criteria for the release are provided above under *gE Antigen Specifications*.



The results for the (b) (4) gE Antigen/AS01$_B$ Adjuvant lots were compared to each other. They were also compared to the (b) (4) Phase 3 clinical gE Antigen/AS01$_B$ Adjuvant lots (see above under *gE Antigen* (b) (4) *Process Development*; however, no in-scope results were provided for comparison). The PPQ lot comparison is shown in the table (only in-scope results are shown). The acceptance criteria for the release testing are provided above under *gE Antigen Specifications*.



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

(b) (4)

(b) (4)

Reviewer's Comments: *The gE Antigen is formulated in Building* (b) (4) *(see below under* Manufacturing Facility Descriptions*) using equipment and procedures used to manufacture other US-licensed products. This building has an existing APS program and therefore the information provided appears to be sufficient to support that the formulation of the gE Antigen is an aseptic process.*

gE Antigen Filling and Lyophilization
APS for the filling and lyophilization operations were performed as described above for the formation operations with (b) (4) units filled, stoppered, lyophilized, capped, inspected and boxed for (b) (4) per APS run and worst-case conditions used (b) (4) The alert limit is (b) (4)) and action limit of (b) (4)).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's Comments: *The gE Antigen is filled, capped and lyophilized using an existing filling line (*(b) (4)*) and lyophilizers in Building* (b) (4) *(see below under* Manufacturing Facility Descriptions*) used to manufacture other US-licensed products. This line has an existing APS program and therefore the information provided appears to be sufficient to support that the filling and lyophilization of the gE Antigen is an aseptic process. However, as described below under* gE Antigen (b) (4)

Furthermore, during the Type C meeting held under INDs 13857 and 13879 of April 14, 2016, GSK was told that aseptic processing within the (b) (4) *filling line* (b) (4) *would need to be re-validated through APS due to these changes. This re-validation is reviewed below under* Review of Amendment 5.

(b) (4)

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

(b) (4)



gE Antigen Container Closure System

gE Antigen Container Closure System Description

The container closure system for the gE Antigen consists of a 3 mL glass vial (Type (b) (4) .) closed with a rubber stopper (b) (4) rubber) and (b) (4) flip-off cap, and is identical to the container closure system used for other commercial vaccines manufactured by GSK. The vial and flip-off cap are the same as used for the $AS01_B$ Adjuvant (see above under *$AS01_B$ Adjuvant Container Closure System*). The stoppers are stated as meeting the (b) (4) requirements and as being tested for appearance (b) (4)

(b) (4) and critical dimensions (b) (4) and being visually inspected before use.

Reviewer's Comments: *It is not clear who supplies the vials and the flip-off caps for the gE Antigen. GSK was therefore asked in an* ***Information Request of June 5, 2017 (comment #3)*** *to clarify the supplier(s). The response is reviewed below under* Review of Amendment 27.

gE Antigen Container Closure System Container Closure Integrity Testing
CCIT for the gE Antigen container closure system consisted of (b) (4) testing (see above under *$AS01_B$ Andjuvant Container Closure System Container Closure Integrity Testing* for a description of the method). (b) (4) lots of gE Antigen (b) (4) were tested at release and at 36, (b) (4). The results for all lots are stated as complying with the (b) (4).

Reviewer's Comments: *The gE Antigen FC contains a* (b) (4) *testing may not be appropriate. GSK was therefore asked in an* ***Information Request of June 5, 2017 (comment #8)*** *to clarify the reason for including the* (b) (4) *and the rationale chosen for the method. The response is reviewed below under* Review of Amendment 27.

gE Antigen Shipping
Shipping of the gE Antigen includes (b) (4) separate transfers:

- (b) (4)
- Shipment of the final product (gE Antigen/$AS01_B$ Adjuvant) by truck, sea freight or plane

See below under *Manufacturing Facility Descriptions* for more information of the manufacturing buildings and what operations are performed in these buildings. The timing of all operations at ambient temperature (transfers to storage room or to labelling and packaging room) are recorded via bar-code reader and tracked in the Warehouse Management System (WMS).

gE Antigen Shipping - (b) (4)
(b) (4)

(b) (4)

The inspected final containers for the final product (gE Antigen/AS01$_B$ Adjuvant) are packaged and placed into cardboard or carton boxes (units) which are grouped into grouping cases or grouping boxes, and freeze indicators are added as appropriate. The grouping cases or grouping boxes are then placed in pallets and transferred to at a warehouse 2-8°C cold room (see below under *Warehouses*).

gE Antigen Shipping – Shipping of Final Product (gE Antigen/AS01$_B$ Adjuvant)
The inter-site transfer of the final product to the shipping preparation facilities includes exit of the pallets containing the final product in grouping cases or grouping boxes from warehouse 2-8°C cold room, transportation by qualified temperature-controlled truck at 2-8° to the shipping preparation facilities, transfer and storage of the pallets containing the final product to the warehouse 2-8°C cold room at shipping preparation facilities where the grouping cases or grouping boxes are moved from pallets for shipping preparation procedures. Shipment of the final product to customers is performed by temperature-controlled truck, plane or sea freight using carriers that are routinely used by GSK for other products.

For final products sent by temperature-controlled truck, the grouping cases or grouping boxes are wrapped and placed onto pallets and with a minimum of (b) (4) temperature recorders ((b) (4)) added per truck and (b) (4) per pallet. For final products sent by plane, the final product is placed into insulated shipping containers (pallet shippers) containing cold packs in either a summer or winter configurations (using SB Small, SB Medium and SB Large shippers) or a universal configuration (using a (b) (4) shipper). Each pallet shipper contains at least (b) (4) temperature recorder, which records the temperature profile during the entire transit time.

Upon arrival at the GSK local destination, all grouping cases are moved into 2-8°C storage. The temperature monitors and indicators of all pallets are checked and if no excursions in are found, the local GSK Quality Assurance department will release the batches. If a temperature excursion outside of the acceptable range occurs, the GSK site´s Quality Assurance Cold Chain department is notified (and appropriate action is taken).

gE Antigen Shipping Qualifications – Temperature-Controlled Trucks
GSK uses exclusively approved carriers. In addition, during routine use and after unloading at a destination, the truck trailer's internal temperature recorded by the temperature recorders is used to verify the adequacy between the temperature recorded and the allowed temperature range throughout the whole transport duration. Temperature-controlled trucks used for (b) (4) road transportation are qualified through an IQ/OQ protocol containing a (b) (4) verification in summer and winter conditions at the working temperature. The truck temperature (b) (4) .

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

(b) (4)



Reviewer's Comments: *The information provided regarding the transfer/shipping of the gE Antigen FC appears to be adequate and acceptable.*

gE Antigen Stability

Samples from gE Antigen FC lots were stored as follows:

(b) (4)



(b) (4)

[redacted]

Reviewer's Comments: *The in-scope stability data and plan for the gE Antigen FC appears to be acceptable. Review of other aspects of stability of the gE Antigen are deferred to the assigned product reviewer.*

Manufacturing Facility Descriptions

Overall Manufacturing Flow by Building

(b) (4)

[redacted]

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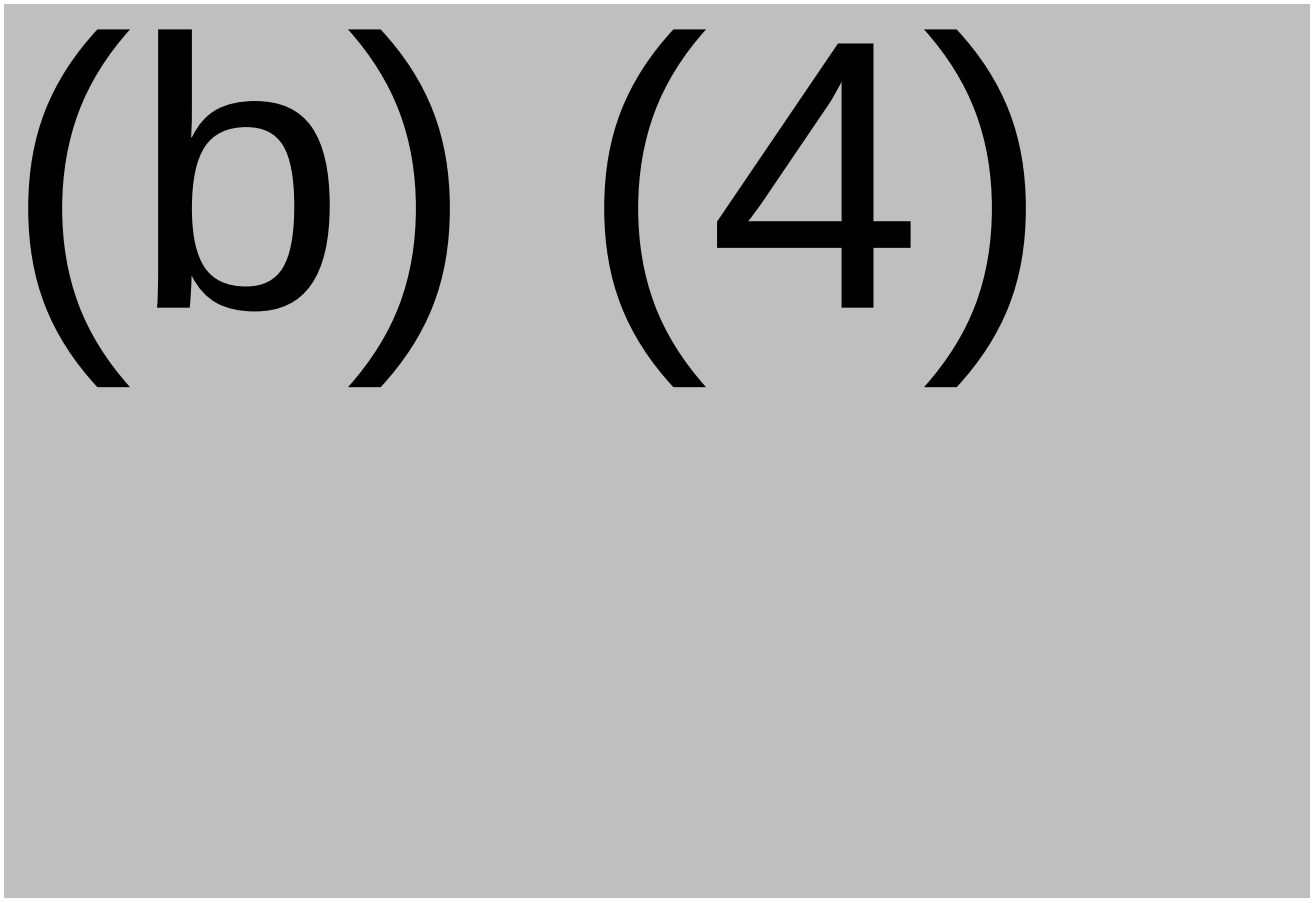
(b) (4) at the (b) (4) site. The visual inspection of the $AS01_B$ Adjuvant FC is performed in Building (b) (4) at the (b) (4) site.

The labeling and packaging of the gE/$AS01_B$ Adjuvant Product is performed either in Buildings (b) (4) at the (b) (4) site or in Building (b) (4) at the (b) (4) site.

Quality Control in-process, sterility and release testing of the gE Antigen (b) (4) are performed in laboratories in Building (b) (4) at the (b) (4) site.

Reviewer's Comments: *Based upon the information provided in the BLA regarding the manufacturing sites, it is not clear if release testing is performed at the Rixensart site as well as what release testing is performed at the* (b) (4) *site. GSK was therefore asked in an* ***Information Request of October 11, 2017 (comment #2)*** *to clarify these issues. The response is reviewed below under* Review of Amendment 54.

Approved Changes to the Manufacturing Facilities Made After the Consistency Lots
The following table describes all of the major changes made to the manufacturing sites since the consistency lots (both gE Antigen and $AS01_B$ Adjuvant) were manufactured (up to submission of this BLA).



Approved Comparability Protocols

The approved CPs shown in the following table are in use in the facilities where the (b) (4) $AS01_B$ Adjuvant and gE Antigen are manufactured.

(b) (4)

(b) (4)

:

(b) (4)

(b) (4)

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(b) (4)

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REVIEW OF AMENDMENT 54

Based upon review of the original submission and the amendment of June 30, 2017 (STN 125614/0/27), an Information Request containing two comments was emailed to GSK on October 11, 2017. GSK responded to this Information Request in an amendment of October 16, 2017 (STN 125614/0/54). GSK's responses to this Information Request are reviewed below. The comments from the Information Request are in **bold** text, GSK's responses are in normal text, and reviewer's comments are in *italicized* text.

1. **Regarding the lyophilization of the gE Antigen, we have the following comments:**

(b) (4)

(b) (4)

Reviewer's Comments: *This response is acceptable.*

2. **Please clarify and describe any release testing performed at the Rixensart, Belgium and (b) (4) facilities.**

   GSK states that no release testing is performed at the Rixensart site, and that one release test for the gE Antigen (b) (4)) and one release test for the $AS01_B$ Adjuvant ((b) (4)) are performed at the (b) (4) site.

   Reviewer's Comments: *This response is acceptable.*