REVIEW MEMORANDUM

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Through:	Hana Golding, Ph.D. Supervisor, DVP, OVRR, CBER, FDA
Through:	Robin Levis, Ph.D., DVP, OVRR, CBER, FDA
Through:	Jerry Weir, Ph.D., DVP, OVRR, CBER, FDA
Subject:	STN125614/0: BLA from GSK for human SHINGRIX; Review of the Chemistry, Manufacturing and Control Information Relevant to AS01B Adjuvant System
Product Name	SHINGRIX, a recombinant varicella zoster virus (VZV) glycoprotein E (gE) vaccine (HZ) combined with GSK's proprietary Adjuvant System AS01B (HZ/su or gE/AS01B)
Applicant	GlaxoSmithKline (GSK) Biologicals
Proposed Indication	HZ/su is a non-live recombinant vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. By preventing herpes zoster, SHINGRIX reduces the overall incidence of postherpetic neuralgia.
Cross-reference(s)	DMF (b) (4) Grey Stoppers) BB-MF (b) (4) (MPL) BB-MF (b) (4) (QS-21, facilities and equipment)

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1. EXECUTIVE SUMMARY, REVIEW HIGHLIGHTS, and RECOMMENDATIONS

SHINGRIX is a sub-unit vaccine consisting of a recombinant varicella zoster virus (VZV) glycoprotein E (gE) antigen combined with GSK's proprietary Adjuvant System AS01B. SHINGRIX is a preservative-free vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older and is referred as HZ/su or gE/AS01B. By preventing herpes zoster, SHINGRIX reduces the overall incidence of post-herpetic neuralgia.

The vaccine is presented in two mono-dose vials: one vial containing the gE protein in a lyophilized form (50 μg/dose) and the second vial containing liquid AS01B Adjuvant System (0.5 mL/dose). The content of the AS01B vial is used to reconstitute the content of the gE vial immediately prior to injection of HZ/su.

The vaccine is to be administered by intramuscular injection in two doses (0.5 mL each); the first dose given at time 0 followed by a second dose anytime between 2 to 6 months.

The gE antigen is a purified recombinant protein produced in Chinese Hamster Ovary (CHO) cells.

SHINGRIX will be the second shingles vaccine approved for use in the USA. The first vaccine for shingles, Zostavax® is prepared based on live attenuated virus, is manufactured by Merck & Co and was approved by FDA in 2008. The Zostavax vaccine does not contain adjuvant.

AS01B DRUG PRODUCT

1.1 GENERAL DESCRIPTION, COMPOSITION, AND MODE OF ACTION OF AS01B ADJUVANT

AS01B components

The AS01B Adjuvant System contains immune enhancers QS-21 (*Quillaja saponaria* Molina, fraction 21) and MPL (3-O-desacyl-4'-monophosphoryl lipid A) combined with liposomes that are prepared using two lipids, DOPC (dioleoyl phosphatidylcholine) and cholesterol in phosphate buffer.

MPL is a detoxified endotoxin obtained from the *Salmonella minnesota* by (b) (4) of the lipopolysaccharide (LPS). The BLA does not provide information on the production of MPL.

MPL in a non-novel excipient that has been previously reviewed by FDA reviewer in the context of GSK AS04 adjuvant included in human prophylactic vaccine Cervarix™ (Human Papilloma virus vaccine) approved in the United States (STN 125259). Cervarix™ contains 50 µg MPL per dose. MPL is produced by (b) (4) doing business as GSK Vaccines in (b) (4). The testing and control of MPL is described in (b) (4), 3-O-desacyl-4'-monophosphoryl lipid A. The cross-reference for BB-MF (b) (4) describing manufacturing of MPL by (b) (4) is included in the BLA (section 3.2.R). To avoid redundancy in the review process, GSK submitted only Certificates of Analysis (COA) for the MPL lots used in the manufacture of AS01B adjuvant as agreed upon during pre-BLA CMC meeting with GSK (July 7 2016; MF (b) (4) Amendment 267).

QS-21 is a saponin purified from the (b) (4) of the South American tree *Quillaja saponaria* Molina. QS-21 powder is manufactured by (b) (4). The BLA contains detailed information about QS-21 powder production and purification.

(b) (4) **cholesterol** is obtained from a (b) (4); it is manufactured by (b) (4) The BLA contains a detailed description of manufacturing of cholesterol for use in AS01B adjuvant.

DOPC is a semi-synthetic phospholipid. It is produced from a (b) (4) DOPC is manufactured by (b) (4). The BLA provides non-proprietary CMC information including Certificate of Analysis from (b) (4) as well as the listing of the control tests performed at GSK with acceptance criteria.

Na_2HPO_4 and KH_2PO_4 are the buffering agents that maintain the target pH of (b) (4) in AS01 Adjuvant.

NaCl in association with the phosphate salts is added to maintain the isotonicity of AS01B Adjuvant.

Table 1 AS01B composition per 0.5 mL dose

Ingredients	Quantity	Function
3-O-desacyl-4'-monophosphoryl lipid A (MPL)	50 µg	Immune enhancer
Purified Quillaja Saponin (QS- 21)	50 µg	Immune enhancer
Dioleoyl phosphatidylcholine (DOPC)	1000 µg	Liposomes membrane constituent

Ingredients	Quantity	Function
Cholesterol	250 µg	Liposomes membrane constituent (b) (4)
Disodium phosphate anhydrous (Na_2HPO_4)	150 µg	Buffering agent
Potassium dihydrogen phosphate (KH_2PO_4)	0.54 mg	Buffering agent
Sodium chloride (NaCl)	4.385 mg	Tonicity agent
Water for injections	(b) (4)	Solvent

AS01B intermediates

Manufacturing of AS01B Adjuvant starts with preparation of (b) (4)

The pharmaceutical form of AS01B Adjuvant System is an opalescent, colorless to pale brownish liquid suspension. The commercial presentation of AS01B is a single-dose vial.

The AS01B final container is a 3 mL glass vial (Type (b) (4) .) closed with rubber stopper and aluminum cap.

AS01 family of adjuvants

AS01B Adjuvant System is part of the AS01 family of Adjuvant Systems that comprises other variants. The most closely related is the AS01E Adjuvant System that contains half the amount of constituents of the AS01B Adjuvant. AS01E adjuvant is included in GSK's malaria vaccine, Mosquirix. The development of AS01B was initiated before that of AS01E and the two variants share the same intermediates (b) (4)

Biological activity/mode of action

AS01B induces a transient activation of the innate immune system by two immune enhancers MPL (Lipid A) (through Toll-Like Receptor 4 expressed by dendritic cells) and by QS-21 through yet an un-known receptor. It is believed that QS-21 signaling involves activity of NLRP3 inflammasome complex. These two agonists activate antigen presenting cells (APC) loaded with antigens in the draining lymph node and enable recruitment of naive $CD4^+$ T cells through enhanced release of cytokines and chemokines by APC. Studies performed by the company indicate that both MPL and QS-21 are required to induce the maximal frequencies of antigen-specific cytokine-producing $CD4^+$ T cells and the highest titers of antigen-specific antibodies.

Important physicochemical properties of AS01B adjuvant

Physicochemical and biological properties of the AS01B Adjuvant System are: pH,(b) (4)

- **pH** AS01B is a buffered Adjuvant System. A pH target (b) (4)

(b) (4)

This review covers the AS01B adjuvant Drug Product, parts of SHINGRIX Drug Product relevant to AS01B adjuvant, and pre-clinical studies of AS01B adjuvant and AS01B components.

1.2 SUMMARY OF THE MANUFACTURING OF AS01B ADJUVANT

Production of intermediates, formulation, filling, QC testing, labeling and packaging of AS01B are performed by GlaxoSmithKline Biologicals at their facility located in (b) (4) Belgium. Labeling, packaging, QC testing, and release may be performed by GSK at their (b) (4) facility or by (b) (4) (doing business as GSK) at their facility in (b) (4) .

Manufacturing of (b) (4)

(b) (4)

(b) (4)

Manufacturing of QS-21 (b) (4)

QS-21 LB (b) (4)

The release specifications of QS-21 (b) (4) commercial lots of QS-21 (b) (4) were analyzed for consistency and all the data were within specifications. The analytical procedures used for QC of QS-21 (b) (4) were all validated.

Novel excipient used for manufacture of QS-21 (b) (4)

QS-21 is a purified immune enhancer derived by (b) (4) purification of (b) (4) the tree *Quillaja saponaria* Molina.

QS-21 appears as a (b) (4) .

QS-21 powder is soluble in water (b) (4)

The QS-21 powder is produced and is subjected to QC testing and stability studies at (b) (4)

The QS-21 manufacturing process starts with (b) (4) of *Quillaja saponaria* Molina tree on (b) (4) QS-21 powder. The manufacturing process is (b) (4) . The QS-21 powder is stored in (b) (4) .

The manufacturing of QS-21 powder is challenging due to major factors: the (b) (4) manufacture QS-21 powder, (b) (4) .

To overcome these complications, the company developed a series of measures to control for (b) (4) These measures include in-process quality decision tests (b) (4)) and in-process monitoring tests for QS-21 and (b) (4) .

The current specifications for QS-21 powder include: (b) (4) .

The (b) (4) amount of QS-21 (b) (4)

Initially QS-21 was manufactured by (b) (4)

QS-21 (b) (4) were used by GSK for development and for nonclinical and clinical studies. QS-21 manufacturing was (b) (4)

At (b) (4) , the QS-21 powder manufacturing was (b) (4)

Stability studies confirmed a (b) (4) shelf-life for QS-21 powder stored at (b) (4).

Potential Impurities in QS-21 powder are: (b) (4)

- (b) (4)
-
- .

Formulation of AS01B DP

The formulation of the AS01B is performed by mixing a (b) (4) solution of phosphate buffer and sodium chloride with WFI (b) (4) depyrogenized and sterilized glass (type (b) (4) vials sealed off with rubber stoppers and capped with flip-off caps.

The container/closure system is identical to that used for other commercial vaccines manufactured by GSK. The AS01B Final Container manufactured at the (b) (4) site is subjected to labeling and is co-packaged with gE final container at GSK facility in (b) (4) BELGIUM or by (b) (4) (doing business as GSK) at their facility in (b) (4).

AS01B Specifications (Final Bulk and Final Container)

AS01B Final Bulk Release Specifications include (b) (4)

Table 2 AS01B Final Container Release Specifications:

Tests (b) (4)	**Acceptance criteria**
Description	Opalescent, colorless to pale brownish liquid (b) (4)
pH	(b) (4)
Volume	
MPL content by (b) (4)	
QS-21 content by (b) (4)	
DOPC content by (b) (4)	
Cholesterol content by (b) (4)	
(b) (4)	

Tests ((b) (4))	Acceptance criteria
(b) (4)	

Batch analysis of AS01B FC lots was performed for lots used in Phase III clinical efficacy studies (Zoster 001, 006, 015, and 022), and for Phase III clinical consistency study (Zoster 007, commercial consistency lots for series A and B). All parameters were within specification.

Company up-date on (b) (4)

On October 6 2017, CBER received a letter from GSK (as part of Amendment 50) describing that during recent review, errors were identified in the data set used for development of (b) (4) . A deviation was opened and a root cause was identified. A new statistical analysis was performed using the corrected data set. The same statistical approach (b) (4) as was used for original specification and the data from the same number of clinical and commercial lots.

Statistical analysis of the corrected data set revealed smaller standard deviation in (b) (4) between lots that leads to (b) (4) : "Between (b) (4) in place of Between (b) (4) (Table 2 above).

It is important to note that all AS01B FC lots produced to date (both clinical and commercial lots) meet this (b) (4) . Therefore, there is no impact on product quality.

Based on these results, the company proposes to change the acceptance criterion for (b) (4) to the limits justified by the analysis of the corrected set of (b) (4) data. This change will be submitted to the FDA by the appropriate regulatory mechanisms. GSK plans to submit a new (b) (4) .

GSK will ensure that all AS01B lots released in the US will meet the (b) (4) of "Between (b) (4) " until the change is (b) (4)

Reviewer: the change in (b) (4) in AS01B in final container and the GSK's plan to (b) (4) in AS01B final container (b) (4) .

AS01B major impurities (b) (4)

(b) (4)

Major steps in the development of AS01B manufacturing

- The manufacturing process of AS01B Adjuvant has been developed through the use of (b) (4) where changes in the manufacturing of (b) (4) and in AS01 formulation were introduced.
- The development of the manufacturing process of AS01B Adjuvant System was initiated at a (b) (4) .
- For the production of (b) (4) These facilities will also be used for subsequent routine commercial campaigns.
- GSK performed multiple comparability studies using batches of AS01B produced using industrialization and commercial processes and demonstrated consistency of the manufacturing process by comparing analytical parameters.

AS01B Final Container stability, shelf-life of FC, and stability indicating parameters

- Long-term, accelerated, and temperature cycling stability studies were performed on AS01B FC lots from (b) (4) . Some of the long-term stability studies are on-going.
- Based on the available stability data generated on AS01B clinical lots and the comparability of the commercial lots to reference lots, GSK proposes a shelf-life of 36 months at 2°C to 8°C for AS01B Adjuvant in 3 mL glass vials. In addition, the AS01B Adjuvant (b) (4) .
- Stability indicating parameters: pH, QS-21 content, Cholesterol content, DOPC content, (b) (4)

The in-use stability of gE/AS01B Reconstituted Vaccine and compatibility studies

- (b) (4)

(b) (4)

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1.3 SUMMARY OF THE CRITICAL STEPS IN THE MANUFACTURE OF AS01B THAT WERE RESOLVED BY THE MANUFACTURER TO ASSURE CONSISTENCY OF PRODUCTION OF STABLE PRODUCT

(b) (4)

1.4 LIST OF INFORMATION REQUESTS (IR) SUBMITTED TO GSK RELATED TO AS01B AND SHINGIX MANUFACTURING PROCESS AND STABILITY STUDIES

1. **In an IR submitted on April 18, 2017 the sponsor was requested to provide the name, source, specification, qualifications including leachables information for the** (b) (4) **filtration systems used in the final filtration of** (b) (4) **Drug Product.**

Company's response (Amendment 19, May 5 2017):

The final filtration of (b) (4) *DP is performed using a* (b) (4) *; the specifications for the* (b) (4) *are detailed in Annex 1, Certificate of Test.*

For AS01B, (b) (4) *studies of the* (b) (4) *are described in m3.2.A.1 Facilities and Equipment, section 1.2.1.3.2 of the document titled AS01* (b) (4) *Chapter 11 Equipment and Associated Qualification – Validation Processes.*

For (b) (4) *study for the* (b) (4) *are described in m3.2.A.1 Facilities and Equipment, section 1.2.1.3.2 of the document entitled* (b) (4) *Chapter 11 Equipment and Associated Qualification – Validation Processes*

Additional qualification work for (b) (4) *has been performed that includes the* (b) (4) *(Annex 2) and* (b) (4) *(Annex 3).*

(b) (4)

Reviewer: I reviewed all information regarding qualification of filters provided in the current Amendment (Annexes 1-8). All information on filter validation provided in the BLA as part of the description of the Facilities and Equipment in m 3.2.A.1 is reviewed by the facilities reviewer, Dr. Jeremy Wally.

2. **In an IR submitted on April 18 2017, the sponsor was requested to clarify how sampling was performed during stability studies of QS-21 (b) (4) stored in (b) (4) as well as the stability data under other conditions.**

Company's response (Amendment 19, May 5 2017, Q2): GSK provided the following clarification regarding sampling of QS-21 (b) (4) *during stability studies*

The QS-21 (b) (4) *lots used for stability studies are stored in* (b) (4)

Reviewer: For the stability evaluation for both QS-21 (b) (4) **, the sponsor uses** (b) (4) **per time point and therefore there is no concern with breaching** (b) (4) **integrity during sampling.**

3. **In an IR submitted on April 18 2017, the sponsor was requested to provide representative Certificates of Analysis for compendial disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride and water for injections, used for formulation of AS01B Drug Product.**

Company's response (Amendment 19, May 5 2017, Q3): The sponsor submitted COA for disodium phosphate anhydrous (Na2HPO4), for monopotassium phosphate (KH2PO4), and for Sodium chloride (NaCl), all manufactured by (b) (4) *.*

Reviewer: The information in all three COAs is acceptable.

4. **In an IR submitted on April 18 2017, the sponsor was requested to clarify whether any testing is performed on AS01B final container at the (b) (4) facility, and provide a list of validation studies on the transferred assays.**

Company's response (Amendment 19, May 5 2017, Q4): The sponsor stated that (b) (4) performs one release test for the gE final container vaccine (b) (4)) and one release test for the AS01B Adjuvant System ((b) (4)). Validation data generated in (b) (4) for these two tests are currently submitted in the SHINGRIX BLA 125614 in m3.2.P.5.3 Validation of Analytical Procedures for the respective drug products. 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.

Reviewer: All information is acceptable

5. **In an IR submitted on June 2 2017, the sponsor was asked to justify the absence of evaluation of pyrogenicity as part of release characterization of AS01B Final Container (FC).**

Company's response (Amendment 27, June 30 2017 Q1): The sponsor indicated that a total of (b) (4) lots were tested for pyrogenicity at release during the development of AS01B Adjuvant System, and results met the acceptance criteria. In addition, pyrogenicity was tested on the (b) (4) commercial lots. All the results were within the acceptance criteria. In order to reduce animal testing, and based on the control strategy implemented by the company, release of commercial lots will no longer include pyrogenicity testing. The (b) (4) is performed for the following components of adjuvant: (b) (4) test cannot be implemented for (b) (4) However, microbial contamination is controlled by (b) (4)

Reviewer: I reviewed the results of pyrogenicity testing that are provided in the BLA (described in the response to IR) and I also reviewed the control strategy implemented by the company to exclude a possibility of microbial contamination of the AS01B during formulation. The provided justification for the lack of pyrogenicity testing is acceptable.

- **This issue was further discussed by reviewers at DVP and DVRPA and it was decided that AS01B falls under CFR 610.15 "Constituent materials" that contains the following statement: "All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality" and since no specific pyrogenicity/endotoxin tests are required for constituent materials, GSK do not need to apply for a waiver regarding testing of AS01B final container for endotoxin.**

6. **In an IR submitted on June 2, 2017, the sponsor was asked to comment on the possibility that the Buffer (b) (4) is tested for (b) (4) and this test is included as part of the release criteria for AS01B FB. Also, the sponsor was requested to clarify the procedure of sampling for testing for (b) (4) as part of the monitoring of the buffer (b) (4)**

Company's response (Amendment 27, June 30, 2017 Q2): The buffer (b) (4) in the AS01B formulation process is a mixture of WFI and buffer PO_4/NaCl. In-process monitoring for (b) (4) is performed on the buffer (b) (4). Since the buffer (b) (4) is not an intermediate, there are no procedures in place to perform

release tests on this buffer or include the in-process test in the release of the resulting final bulk. In response to the second part of the question, the sponsor clarified that the sample is collected from a mixture of WFI, NaCl, and phosphate buffer by (b) (4) *is performed using an analytical method in compliance with* (b) (4)

Reviewer: I reviewed the response provided by the sponsor and found all information acceptable.

7. **In an IR submitted on June 2, 2017, the sponsor was asked if they considered developing a protocol for detection of endotoxin in the AS01B FC using a strategy that** (b) (4)

Company's response (Amendment 27, June 30, Q3): The company argued that using (b) (4) *AS01B will* (b) (4) *. Therefore, the presence of MPL (a* (b) (4) *as part of AS01B adjuvant will lead to a false positive result in the* (b) (4) *test and* (b) (4) *will not be detected. Based on this limitation, the company has put in place a control strategy to ensure absence of* (b) (4) *contamination in the AS01$_B$ manufacturing process. It is based on the control of all incoming materials and intermediate steps with* (b) (4) *tests. This strategy is described in detail in IRs 5 and 6.*

Reviewer: I reviewed the clarification provided by the company related to the presence of MPL in AS01B that will not allow detection of (b) (4) **, and I accept the response.**

8. **In IR submitted on June 5, the sponsor was requested to provide information on the source of the vials and flip-off cups used for AS101B adjuvant and gE antigen**

Company's response (Amendment 27, June 30, Q3): GSK clarified that the glass vials are supplied by (b) (4) *; the Flip-off caps are supplied by* (b) (4) *The different suppliers of glass vials may be used interchangeably.*

Company's response (Amendment 30, July 12, Q3): In Table 2, GSK provided a list of approved vaccines that were manufactured by GSK and that used the same glass containers as those that will be used to store gE DP and AS01B adjuvant. The following vaccines are listed: dTpA (Boostrix), DTPa (Infanrix), DTPa-IPV (Kinrix), HAB adult vaccine (Twinrix), HAV 1440 adult vaccine (Havrix), HAV 720 pediatric vaccine (Havrix), HBV adult and HBV pediatric vaccine (Engerix-B), Hib-MenCY-TT vaccine (Menhibrix), Hib vaccine (Hiberix), Human Rotavirus lyophilised vaccine (Rotarix Lyo), AS03 FC in Flu Q-H5N1 Pandemic Indonesia vaccine

Reviewer: I reviewed the provided list of suppliers for glass vials and the list of approved vaccines that use the same glass vials for final container. All information is acceptable.

9. **In an IR submitted on June 8, the sponsor was requested to comment on the instruction for injection of Shingrix within 6 hours after reconstitution of antigen with adjuvant per information provided in the Carton-Container label. In addition, the reviewer noted that protocols for Zoster-006 and Zoster-022 provide instructions to use Shingrix within 2 hours after reconstitution. The sponsor was requested to explain the rationale for using the reconstituted vaccine within 6 hours.**

Company's response (Amendment 27, June 30): GSK's acknowledged that the allowed in-use Hold time for Shingrix increased as clinical development progressed, and thus the initial recommendation of administering Shingrix was expanded from within two hours to within six hours of reconstitution. The

recommendation to administer Shingrix within 6 hours of reconstitution was based on in-use stability data generated during development (up to (b) (4) *hours), and on the WHO multi-dose vial policy, which recommends limiting the use of opened vials to within six hours to ensure sterility.*

Reviewer: I reviewed the information provided by GSK in response to the IR. Additionally, the stability data of reconstituted vaccine confirm its stability for up to (b) (4) **hours at** (b) (4) **(reviewed and summarized by reviewer as part of stability reports). Therefore, I consider the instruction for usage of reconstituted vaccine within 6 h after reconstitution to be acceptable.**

10. **In an IR submitted on June 27, the sponsor was requested to clarify whether the same** (b) (4) **with** (b) (4) **screw caps are used for storage of the QS21** (b) (4) **and for storage of the** (b) (4)

Company's response (Amendment 30, July 12): GSK clarified that the same (b) (4) *closed with* (b) (4) *screw caps are used for* (b) (4) *batches. The* (b) (4) *of the* (b) (4) *is different:* (b) (4) *batches, both from the same supplier (i.e.* (b) (4) *).*

Reviewer: all information is acceptable

11. **In an IR submitted on June 27, the sponsor was requested to provide details of the** (b) (4) **study for** (b) (4) **rubber stoppers used in glass vials for packaging of AS01B DP.**

Company's response (Amendment 30, July 12): A (b) (4) *study was performed to assess the use of the* (b) (4) *grey stoppers* (b) (4) *rubber stopper) as closure system for AS01B Adjuvant. In this study, the comparison of the* (b) (4) *rubber stopper was compared with the* (b) (4) *of AS01B Adjuvant System. In their response, GSK provided the following details (per request from CBER): lots that were tested, storage conditions, and results.*

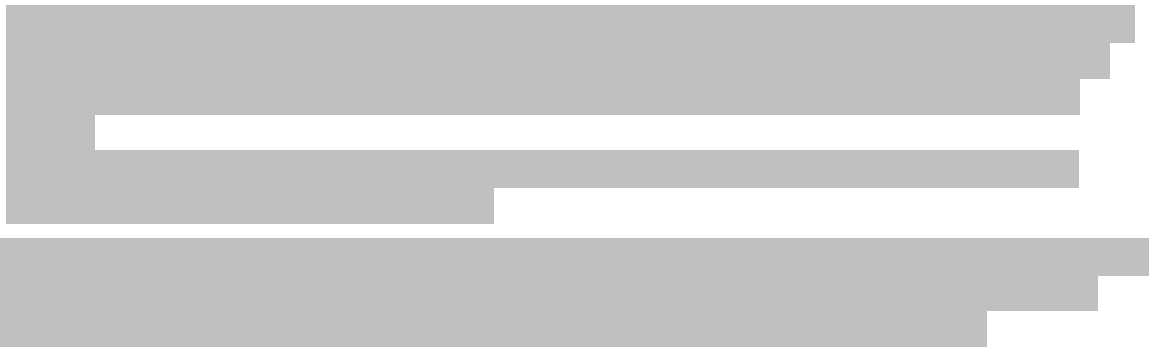
The aim of this analytical study was to compare the (b) (4) *of a "ready-to-use"* (b) (4) *rubber stopper* (b) (4) *grey) with the* (b) (4) *of adjuvant AS01B that has been in long-term contact* (b) (4) *months) with the* (b) (4) *. The samples of the rubber stopper were* (b) (4) *using the following methods:* (b) (4)

Testing approach in brief: (b) (4)

Results:

- (b) (4)

(b) (4)



Consequently, the levels of these chemical species that may be present in a vaccine dose are considered unlikely to be of significant toxicological concern.

Reviewer: I reviewed the detailed protocol of the (b) (4) study of (b) (4) AS01B FC closed using (b) (4) grey stoppers. The protocol and complete data with figures and (b) (4) is provided in Annex 1 in Amendment 30. The provided information is sufficient to conclude that there is no safety concern related to usage of (b) (4) grey stoppers as container closure system for AS01B FC.

12. **In an IR submitted on June 27, the sponsor was requested to provide information on any follow up regarding detection of (b) (4) originating from (b) (4) rubber stoppers during QC analysis of QS-21 content in AS01B DP. The sponsor was also requested to clarify whether the same stoppers were used in final containers of other approved vaccines**

Company's response (Amendment 30, July 12, Q 002b): (b) (4) grey stoppers (b) (4) rubber stopper) are used in the following aqueous vaccines: Engerix-B, Havrix, Infanrix, Infanrix IPV, and Boostrix. The rubber stoppers are also used as closure system for the AS03 Adjuvant System.

Reviewer: information noted

13. **In an IR submitted on August 2, the sponsor was requested to provide (in addition to process-related impurities listed in section P.5.5) a list of all materials such as materials used as (b) (4) for assessment of (b) (4) for $AS01_B$ DP and materials used in (b) (4) for storage of (b) (4) filtration systems and provide an assessment about their amounts in each of the final DPs.**

Company's response (Amendment 39, August 29, Q 001): The filters used in the manufacturing of (b) (4), QS-21 (b) (4) and formulation of AS01B are single use and they are not treated prior to their use in the filtration step. The integrity of the filter is tested after use and is described in the BLA. (b) (4) (b) (4) is the solvent used in the manufacturing process of (b) (4). The highest residual (b) (4) content observed in a (b) (4) in a development lot (b) (4) and (b) (4) in a commercial lot (b) (4). These values are well below the acceptable limit of (b) (4) for Class (b) residual solvents stated in the EMA guideline "Impurities: Guideline for Residual Solvents" ICH topic Q3C(R4). No other solvents than water for injection are used in the manufacturing process of QS-21 (b) (4) and AS01B (b) (4).

Several solvents are used during the manufacturing process of MPL (b) (4) Similarly, several solvents are used for the manufacturing process of QS-21 (b) (4) Due to robust solvent control and the low

daily dose of MPL and of QS-21, it is assessed that there is no quality risk to AS01 or vaccine products associated with any of the solvents used in the MPL (b) (4) *or in the QS-21 powder manufacturing process. Removal of* (b) (4) *from the equipment has been demonstrated by cleaning validation studies for each piece of equipment. It is concluded that the potential for MPL* (b) (4) *or of QS-21* (b) (4) *to contribute undesired substances to AS01 or vaccine drug products is extremely low, and the risk is further mitigated by the low MPL dose in the vaccine.*

Reviewer: I reviewed the information on additional in-process related impurities and assessment on their potential presence in the AS01 DP. I concur with the company's assessment that the potential for MPL (b) (4) **and for QS-21** (b) (4) **to contribute undesired substances to AS01B is extremely low.**

14. **In an IR submitted on August 2, the sponsor was requested to provide the Certificate of Analysis for a** (b) (4) **lot used for manufacture of QS-21 powder**

Company's response (Amendment 39, August 29, Q 002): The certificate of Analysis (COA) was provided for a (b) (4) *Lot* (b) (4) *manufactured in November 2016.*

Reviewer: I reviewed the COA of Lot (b) (4) **and I confirm that all parameters are within specification.**

1.5 HIGHLIGHTS OF THE REVIEW OF AS01B ADJUVANT SYSTEM

1. SHINGRIX (gE/AS01B) is the first shingles vaccine that contains adjuvant. The currently used FDA-approved shingles vaccine, Zostavax, is a live virus attenuated vaccine that does not include adjuvant. AS01B adjuvant is not used in any approved vaccines and it will be approved in the context of SHINGRIX for the first time.
2. AS01B is what is called a "combinational" adjuvant. This definition is based on the nature of this product that contains two immune enhancers, monosphoryl lipid A (MPL) and QS-21 saponin; each of them alone can enhance immune response to vaccine antigen. The rational for including QS-21 is based on studies that showed the ability of QS-21 to enhance cell-mediated immunity. To achieve optimal response to gE antigen, GSK combined MPL and QS-21 and formulated them with liposomes to assure delivery to antigen presenting cells. Liposomes in AS01B are bilayer vesicles that contain semi-synthetic phospholipid, DOPC and (b) (4) cholesterol. The AS01B adjuvant is provided in a separate vial and is used to reconstitute the lyophilized recombinant gE protein immediately prior to injection.
3. MPL is derived from *Salmonella minnesota* and is used in GSK's adjuvant AS04 incorporated in Human Papillomavirus vaccine (Cervarix) approved by FDA in 2009. Liposomes similar to the ones developed by GSK for AS01B, are widely used for targeted drug delivery. <u>The true novelty of AS01B adjuvant is the incorporation of QS-21 in the formulation.</u>
4. QS-21 is a saponin purified from the (b) (4) of the South American tree *Quillaja saponaria* Molina. QS-21 powder is manufactured from the aqueous extract of the tree (b) (4) by (b) (4) purification. During early stages of development, it was determined that the immune potentiating quality of the (b) (4) from *Quillaja saponaria* was mediated by several (b) (4) collected during (b) (4) purification. Unlike other fractions, fraction 21 showed immune enhancing activity without toxicity. Later on it was discovered that QS-21 contains (b) (4) . Initial development of QS-21 as adjuvant was performed by (b) (4) that established optimal composition of QS-21 (b) (4)

This composition is preserved at (b) (4) that manufactures QS-21 powder for GSK. The company made considerable investment in refining the (b) (4) purification of QS-21 to obtain consistent product. The consistency of the (b) (4) is achieved by using (b) (4) to obtain the desired composition of saponin (b) (4) in QS-21 powder.

5. It is important to note, that similar to other saponins, QS-21 alone possesses hemolytic activity due to its ability to (b) (4) . In AS01B, QS-21 (b) (4) is achieved through the interaction of QS-21 with (b) (4) The absence of hemolytic activity in the AS01B is demonstrated by testing in (b) (4)
6. The critical parameters for the production of the (b) (4) QS-21 (b) (4) AS01B adjuvant were validated according to defined validation criteria and are presented in the BLA. The consistency and robustness of the production process is demonstrated through analyses of the process data collected during the manufacture as well as through the analysis of Quality Control data for the release of (b) (4) QS-21 (b) (4) AS01B Final Container.
7. The manufacturing process for the AS01B adjuvant and of (b) (4) QS-21 (b) (4) has been modified during development, and data were submitted that demonstrated that batches manufactured according to revised processes have comparable physico-chemical properties.
8. The consistency of the manufacturing of AS01B was confirmed in Phase III clinical consistency study Zoster-007 using (b) (4) GMP industrialization batches of AS01B adjuvant manufactured at (b) (4) & (b) (4) facilities. The AS01B consistency lots were combined with (b) (4) consistency lots of gE DP.
9. Regarding the Stability Protocols for AS01B, the analytical methods used are the same as the Quality Control and characterization methods used for release testing of MPL, DOPC, cholesterol, and for QS-21 in (b) (4) and QS-21 (b) (4) .
10. Based on real-time stability data, GSK proposes a shelf-life of 36 months for AS01B Adjuvant in 3 mL glass vials stored at 2°C to 8°C.

1.6 CONCLUSION AND RECOMMENDATION

In summary, the CMC information and data relevant to the AS01B system in SHINGRIX that have been presented in this BLA are complete and adequate to demonstrate that the AS01B adjuvant is manufactured under GMP by a validated process and the AS01B adjuvant meets generally accepted standards of purity and quality as required for an adjuvant or constituent material as per 21 CFR 610.15. Overall, the AS01B-relevant CMC information presented in the Quality Module of the BLA supports the approval of the BLA for manufacture of SHINGRIX (gE/AS01B).

I recommend approval of the BLA for SHINGRIX.

2. FULL REVIEW OF THE AS01B ADJUVANT DRUG PRODUCT

THE FOLLOWING SECTIONS WERE ASSIGNED TO AND WERE REVIEWED BY THIS PRODUCT REVIEWER (ALL IN 3.2.P DRUG PRODUCT AS01B ADJUVANT SYSTEM)

- Description and Composition of the Drug Product [3.2.P.1]
- Pharmaceutical Development [3.2.P.2]
  - Components of the Drug Product [3.2.P.2.1]
    - Drug Substance [3.2.P.2.1.1]
    - Excipients [3.2.P.2.1.2]
  - Drug product [3.2.P.2.2]
    - Formulation Development Summary [3.2.P.2.2.1]
    - Justification for Overages [3.2.P.2.2.2]
    - Physiochemical and Biological Properties [3.2.P.2.2.3]
  - Manufacturing Process Development [3.2.P.2.3]
  - Container Closure System [3.2.P.2.4]
  - Compatibility [3.2.P.2.6]
- Manufacture [3.2.P.3]
  - Manufacturer(s) [3.2.P.3.1]
  - Batch Formula [3.2.P.3.2]
  - Description of Manufacturing Process and Controls [3.2.P.3.3]
  - Controls of Critical Steps and Intermediates [3.2.P.3.4]
  - Process Validation and/or Evaluation [3.2.P.3.5]
- Control of Excipients [3.2.P.4]
  - Specifications [3.2.P.4.1]
  - Analytical Procedures [3.2.P.4.2]
  - Validation of Analytical Procedures [3.2.P.4.3]
  - Justification of Specifications [3.2.P.4.4]
  - Novel Excipients [3.2.P.4.6]
- Control of Drug Product [3.2.P.5]
  - Specifications of Drug Product [3.2.P.5.1]
  - Analytical Procedures [3.2.P.5.2]
  - Batch Analyses [3.2.P.5.4]
  - Characterization of Impurities [3.2.P.5.5]
  - Justification of Specification [3.2.P.5.6]
- Reference Standards or Materials [3.2.P.6]
- Container Closure System [3.2.P.7]
  - Specifications (vial, elastomer, drawings)
  - Materials of construction
  - Suitability
  - Leachables and extractables
- Stability [3.2.P.8]
  - Stability Summary and Conclusions [3.2.P.8.1]
  - Post-approval Protocol and Commitment [3.2.P.8.2]

- Real-time Stability Data [3.2.P.8.3]

o Novel excipients [3.2.A.3]
o Executed batch records
o Lot Release Protocol template

Literature references and copies [3.3]

PRE-CLINICAL STUDIES (AS01B ADJUVANT AND AS01B ADJUVANT COMPONENTS) ASSIGNED AND REVIEWED BY THIS PRODUCT REVIEWER

PRIMARY PHARMACODYNAMICS [4.2.1.1]

- LIMS20080769-20080771-20090756: Role of (b) (4) in AS01 adjuvant effect
- LIMS20090807-20100654: Impact of (b) (4) injection of AS01B and gE on innate and gE-specific adaptive immune responses in mice effect
- LIMS20110060-20110061: Contribution of MPL and QS-21 in AS01 effect on antibody and T cell response
- LIMS20110202-20080761: Contribution of MPL and QS-21 in AS01 effect on local innate response
- LIMS20110226: Characterization of Local innate response induced by AS01
- LIMS20110310: Local distribution of AS01B at the injection site administered alone and in combination with the gE antigen
- LIM2S0120490-20120517: Contribution of MPL and QS-21 in AS01 effect on antigen presentation by activated antigen presenting cells
- VR2013MPL01: In vivo deficiency in (b) (4) innate and adaptive response induced by MPL
- VR2013MPL02: In vitro comparison of MPL and (b) (4) ability to induce (b) (4) cytokines and (b) (4) downstream pathways
- VR2013QS-21-01: In-vitro characterization of QS-21 ability to activate human immune cells
- VR2013QS-21-02: In vitro evaluation of molecular pathways of QS-21 interaction with immune cells
- VR2013QS-21-03: Key role of endocytosis in the immune-stimulatory properties of QS21

PHARMACOKINETICS/BIODISTIBUTION (4.2.2.3)

- (b) (4) -MPL: Pharmacokinetics, distribution and excretion of (b) (4) following intramuscular administration to the rat
- (b) (4) MPL: Pharmacokinetics, distribution and intravenous administration to the rat
- GSK-CH-01-09: Comparison of the in vivo fate in mice of (b) (4) -DOPC and (b) (4) -QS-21 formulated in AS01B given intramuscularly
- GSK-CH-01-15: Biodistribution of (b) (4) (in AS01-like formulation) given once intramuscularly in (b) (4) mice
- (b) (4) : Pilot distribution study of (b) (4) QS-21 following intramuscular administration to (b) (4) White Rabbits

GENERAL INFORMATION, NOMENCLATURE, STRUCTURE, AND PROPERTIES OF AS01B ADJUVANT

In the monograph, the $AS01_B$ adjuvant is referred to as a diluent for reconstitution of the vaccine.

AS01B does not contain any Drug Substance.

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.

- QS-21 is a natural saponin molecule (triterpene glycoside) obtained from the (b) (4) of the tree *Quillaja saponaria* Molina. QS-21 is manufactured by (b) (4)
- MPL (b) (4) is a (b) (4) of the parent lipopolysaccharide (LPS) from the Gram-negative bacterium *Salmonella minnesota*.
- The liposomes are prepared using dioleoyl phosphatidylcholine (DOPC) and cholesterol.

The pharmaceutical form of $AS01_B$ Adjuvant System is an opalescent, colorless to pale brownish liquid suspension. The commercial presentation of $AS01_B$ is a single-dose vial.

The $AS01_B$ final container is a 3 mL glass vial (Type (b) (4) .) closed with rubber stopper and (b) (4) cap.

Brief description of $AS01_B$ components

All components of $AS01_B$ adjuvant are considered excipients

- **MPL** [3-O-desacyl-4'-Monophosphoryl Lipid A (MLA)], is obtained by (b) (4) of the lipopolysaccharide (LPS) of the *Salmonella minnesota* (b) (4) In the AS01 Adjuvant System, MPL enhances the immune response to the antigen(s) in the vaccine.
- **QS-21** is a saponin purified from the (b) (4) of the South American tree *Quillaja saponaria* Molina. In the AS01 Adjuvant System, QS-21 enhances the immune response to the antigen(s) in the vaccine.
- **DOPC** [1, 2-Dioleoyl-sn-glycero-3-phosphocholine] is a semi-synthetic phospholipid. It is produced from a (b) (4) . DOPC is one of the two components forming the bilayers of the liposomal membrane.
- **Cholesterol is a** (b) (4) cholesterol. The original starting material for this product is (b) (4) . In AS01, cholesterol is one of two components of the liposomal membrane serving to increase the (b) (4) . In addition, cholesterol interacts with QS-21 resulting in (b) (4)
- **Na_2HPO_4**, and **KH_2PO_4** are the buffering agents that maintain the target pH of (b) (4) in AS01 Adjuvant.
- **NaCl** in association with the phosphate salts is added to maintain the isotonicity of AS01 Adjuvant.

Composition of $AS01_B$ Drug Product

Table 3 Composition of the $AS01_B$ Adjuvant Drug Product

Ingredients	Quantity (per 0.5 ml dose)[1]	Function	Reference/ Monograph standard
3-O-desacyl-4'-monophosphoryl lipid A (MPL)	50 μg	Immune enhancer	(b) (4)
Purified Quillaja Saponin[2] (QS- 21)	50 μg	Immune enhancer	
Dioleoyl phosphatidylcholine (DOPC)	1000 μg	Liposomes membrane constituent	
Cholesterol	250 μg	Liposomes membrane constituent and (b) (4)	
Disodium phosphate anhydrous (Na_2HPO_4)	150 μg	Buffering agent	
Potassium dihydrogen phosphate (KH_2PO_4)	0.54 mg	Buffering agent	
Sodium chloride (NaCl)	4.385 mg	Tonicity agent	
Water for injections	(b) (4)	Solvent	

(b) (4)

[2]Purified Quillaja Saponin is the full name of QS-21

2.1 AS01B DRUG PRODUCT PROPERTIES

The AS01B liposomes-based Adjuvant System contains QS-21 and MPL immune enhancers. The ability of the AS01 family of adjuvants to enhance immune responses to antigens was confirmed in nonclinical and clinical studies. During vaccine dose preparation, the AS01B Adjuvant is used to reconstitute the lyophilized antigen.

Below I provide review of the section describing the physicochemical and biological properties of AS01B and the tests performed to characterize the (b) (4) as well as the AS01B Adjuvant System (b) (4) Final Container (FC).

2.1.1 Biological activity

AS01 induces a transient activation of the innate immune system via signaling pathways specific to MPL (Toll-Like Receptor 4) and QS-21 (including the NLRP3 inflammasome). This creates a local environment that favors the activation of antigen-presenting cells loaded with antigens in the draining lymph node where they can activate recently recruited naive $CD4^+$ T cells. Preclinical study results in the BLA indicate that each of the immune enhancers present in AS01 (QS-21 and MPL) are required to induce potent gE-specific $CD4^+$ T cell and humoral responses. The data supports the notion that both MPL and QS-21 are required to induce the maximal frequencies of antigen-specific cytokine-producing $CD4^+$ T cells and the highest titers of antigen-specific antibodies.

2.1.2 Physicochemical Properties

Physicochemical and biological properties of the AS01B Adjuvant System are: pH, (b) (4)

(b) (4)

- (b) (4)

(b) (4)

2.2 AS01B MANUFACTURERS, BATCH FORMULA, AND STEPS OF THE MANUFACTURING PROCESS

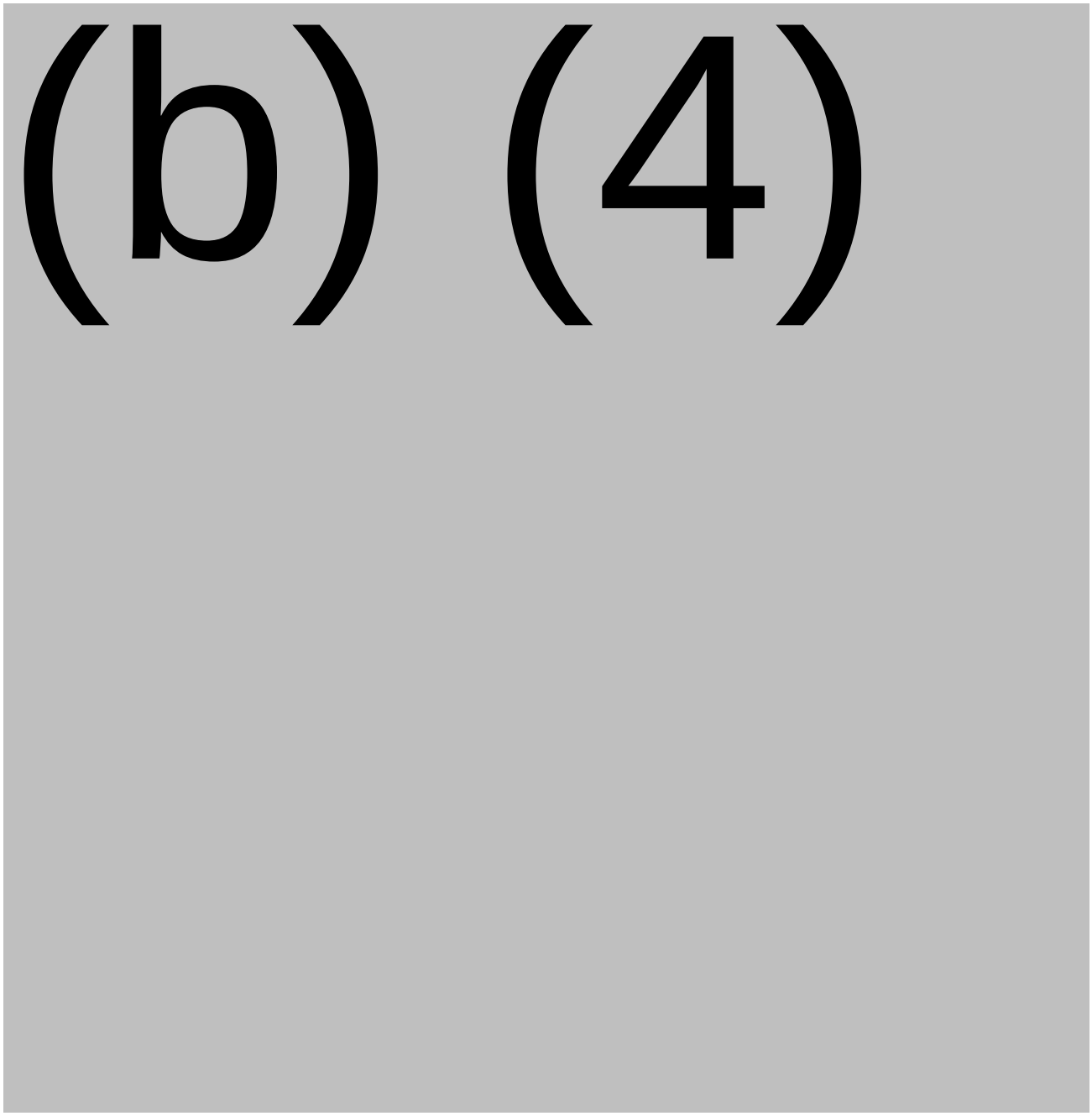
Table 4 AS01B manufacturers

Manufacturers	**Responsibilities**
GlaxoSmithKline Biologicals S.A. (b) (4) BELGIUM	Production of intermediates
GlaxoSmithKline Biologicals s.a. (b) (4) BELGIUM	Formulation, filling, QC testing, labelling and packaging operations
(b) (4) GlaxoSmithKline Vaccines (b) (4)	Labelling and packaging operations, QC testing, QA release
GlaxoSmithKline Biologicals s.a. Rue de l'Institut 89 1330 Rixensart BELGIUM	QA release

Dba, Doing business as; s.a. Société anonyme (plc: public limited company)

AS01B Batch Formula

Table 5 Batch formula for AS01B Adjuvant System lots (b) (4)



AS01B Steps of the Manufacturing Process

The manufacturing process of the $AS01_B$ Adjuvant System consists of the following steps (sections in brackets refer to the sections in BLA):

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

LABELING AND PACKAGING OF THE AS01B FINAL CONTAINER (FINAL PRODUCT)

The commercial AS01B Final Container (FC) vial is labelled with a single 5-digit alpha numeric lot number according to Company's internal procedures. The lot number is generated randomly by the SAP system and consists of both letters and numbers.

The batch numbering system for the gE Lyophilised FC vial and for the gE Lyophilized vial packed together with the AS01B vial is described in 3.2.P.3.3 Batch numbering system gE Lyo.

The vaccine vial is labelled with the antigen expiration date; the adjuvant vial is labelled with the adjuvant expiration date; the combo box is labelled with the expiration date corresponding to the earliest of the antigen and the adjuvant system expiration dates.

Note from the reviewer regarding the order of the current review*: In the current review, the description of AS01B manufacturing process is organized as follows:*

(b) (4)

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

- (b) (4)

Conclusion

All the data presented above show that the container closure system is suitable for its intended use.

2.5 FORMULATION OF AS01B DP

Process Summary

The formulation of the Adjuvant System $AS01_B$ is performed by mixing (b) (4) solution of phosphate buffer and sodium chloride with water for injection (WFI) (b) (4)

2.5.1 AS01B (b) (4) Formulation and Filling of the Final Container (FC)

(b) (4)

- .

(b) (4)

SOLUTIONS and MATERIALS

Table 18 Solutions and materials used during formulation of AS01B

Solutions/materials	Composition	Final* concentration / amount of ingredients	Analytical references
Water for injections	N/A	(b) (4)	
Phosphate buffer Na/K PO_4 (b) (4)	Na_2HPO_4 KH_2PO_4		
NaCl (b) (4)	NaCl		

*Final concentration of the buffer prior to formulation

Reviewer: The BLA did not contain Certificates of Analyses (CoA) of compendial materials disodium phosphate anhydrous, potassium dihydrogen phosphate, sodium chloride used for formulation of AS01B. An IR was submitted on April 18, 2017.

Company's up-date: In response to IR, the sponsor submitted all requested CoAs (May 5, 2017)

FILLING AND LABELING OF AS01B FINAL CONTAINER

Filling of the Final Container

- The $AS01_B$ (b) (4) is aseptically filled under Class (b) (4) /Grade (b) (4) depyrogenized and sterilized glass (type) vials using an automatic filling/stoppering machine under (b) (4). The container/closure system is identical to that used for other commercial vaccines manufactured by GSK.

- Glass vials are sealed off with rubber stoppers and capped with flip-off caps. Glass vials and stoppers are received from the manufacturer, inspected, and are released for use by Quality Assurance (QA).
- Released glass vials are (b) (4) are sterilized and depyrogenized (b) (4)
- After filling, the vials are automatically stoppered. Stoppered vials are sealed with color-coded flip-off caps allowing product identification.

  The target fill volume is a process parameter. It is measured at pre-determined intervals throughout filling operations

Inspection and storage

- Assembled containers are visually inspected for fill volume, particles and conformity of the container closure system. Non-conforming containers are rejected, accounted for, and discarded.
- A defined number of containers are sampled from each batch for QC release testing.
- Inspected and approved containers are placed in boxes, palletized, and stored at the warehouse (2 to 8°C) for labeling and packaging.

Labeling and Packaging

- The $AS01_B$ Final Container manufactured at the (b) (4) site may be transported to (b) (4) site to be labelled and co-packed with the gE Final Container as described below. Alternatively, they may be packaged at the (b) (4) site.
- Vials are labelled automatically on a labelling machine.
- Labels are overprinted with lot number and expiry date and then affixed to the vials. The labelled vials are then introduced into a cardboard box simultaneously with a product information insert (leaflet).

- Lot number and expiry date are printed on each individual box. Cardboard boxes are visually inspected and placed in grouping boxes. Boxes are identified, palletized and stored at 2°C to 8°C before release and expedition.

2.5.2 AS01B Specifications (Final Bulk and Final Container)

The specifications for the routine release of AS01B Adjuvant System, at final bulk and final container levels, are described in the Company's (b) (4) , respectively. An overview of the quality control testing is summarized in Tables 19 and 20 (based on Table 1 and Table 2 in 3.2.P.5.1 AS01B Specifications).

(b) (4)

Table 20 AS01B DP Final Container release Specifications

Tests (b) (4))	**Acceptance criteria**
Description	Opalescent, colorless to pale brownish liquid (b) (4)
pH	(b) (4)
Volume	
MPL content by (b) (4)	
QS-21 content by (b) (4)	
DOPC content by (b) (4)	
Cholesterol content by (b) (4)	
(b) (4)	

Tests ((b) (4)	Acceptance criteria
(b) (4)	

(b) (4)

2.5.3 AS01B Analytical Procedures

Table 21 Analytical procedures for testing of the AS01B FC

Tests	Reference
Description	In-house
pH	(b) (4) .
Volume of injection	The determination of volume for injection is aligned on the current (b) (4) .
MPL content by (b) (4)	In-house
QS-21 content by (b) (4)	In-house
DOPC content by (b) (4)	In-house
Cholesterol content by (b) (4)	In-house
QS-21-(b) (4)	In-house
(b) (4)	

Summary of the in-house analytical procedures is provided below.

Description: Appearance of the product is visually examined. The product is visually examined for mainly these characteristics: Presence or not of particles, Opalescence, Color, Sedimentation (if applicable)

MPL content: (b) (4)

(b) (4)

QS-21 content: (b) (4)

DOPC content: (b) (4)

.

Cholesterol content: (b) (4)

.

(b) (4)

(b) (4)

Validation of analytical procedures is reviewed in detail by DBSQ reviewers.

2.5.4 AS01B Batch Analysis

Table 22 List of Manufacture sites, batch size, and clinical use of AS01B FC lots

AS01B Final Bulk Lots	AS01B Final Container Lots	Approximate Batch size	Filling date	Manufacturing site	Clinical Use	Use in Stability Studies	Series
DA01A023	DA01A023A	(b) (4)			Phase III clinical efficacy (Zoster-001, -006, -015 and -022)	Yes	(b) (4)
DA01A027	DA01A027A				Phase III clinical efficacy (Zoster-006 and -022)	Yes	
DA01A029	DA01A029A						
(b) (4)					Not used in Zoster clinical studies	Yes	
(b) (4)							
(b) (4)							
DA01A056	DA01A056A				Phase III clinical consistency (Zoster-007)	No	
DA01A058	DA01A058A						
DA01A059	DA01A059B						
(b) (4)					Commercial consistency lots (b) (4) Not used in zoster clinical studies	Yes	
(b) (4)							
(b) (4)							
(b) (4)					Commercial consistency lots (b) (4) To be used in future zoster clinical studies	Yes	
(b) (4)							
(b) (4)							

Reviewer: The results of individual batches (final bulk and final container) listed in the Table 22 above for (b) (4) are provided in 3.2.P.5.4 of the BLA and are all within acceptance criteria.

2.5.5 AS01B Impurities

The impurities that could potentially be present in AS01 Adjuvant System are listed in Table 23 together with the control strategy.

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

(b) (4)

Reviewer: The control of potential impurities is acceptable.

2.5.6 AS01B Justification of Specifications

The specifications for AS01B FB and final container FC have been established. Sterility tests of AS01B FB and AS01B FC and pH measurement, (b) (4) , and volume tests on FC are performed according to (b) (4) requirements.

SUMMARY OF THE JUSTIFICATION OF SPECIFICATIONS FOR AS01B FC (from Table 3 in 3.P.5.6)

- *Description*; Acceptance criteria: Opalescent, colorless to pale brownish liquid (b) (4)
- *pH*; Acceptance criteria: Between (b) (4)
    - Justification: AS01B Adjuvant System is a buffered solution. The pH specification range corresponds to the target value of pH (b) (4) defined by the phosphate buffered saline in the AS01B.
- *Volume*; Acceptance criteria: Between (b) (4) ml
    - Justification: The proposed range was defined to ensure that a single nominal dose of 0.5 mL of the final product is delivered after reconstitution of the lyophilized antigen with the AS01B Adjuvant. The proposed range is based on a (b) (4)
- *MPL content by* (b) (4) Acceptance criteria: Between (b) (4)
    - Justification: The proposed acceptance criteria correspond to the (b) (4)
- *QS-21 content by* (b) (4); Acceptance criteria: Between (b) (4)

- Justification: The proposed acceptance criteria correspond to the (b) (4)

- *DOPC content by* (b) (4); Acceptance criteria: Between (b) (4)
  - Justification: The proposed acceptance criteria correspond to the (b) (4)

- *Cholesterol content by* (b) (4) Acceptance criteria: Between (b) (4)
  - Justification: The proposed acceptance criteria correspond to (b) (4)

  - (b) (4)

AS01B FC lots used for the determination of specifications are listed. They include clinical lots from (b) (4)

The subsequent sections describe the levels of each parameter and illustrate the statistical analysis used to determine acceptance criteria using these reference lots.

Reviewer: All information is clearly written and is acceptable.

REFERENCE STANDARDS OR MATERIALS

- Quality Control (QC) release tests used for the testing of AS01 Adjuvant System FC lot for calibration and/or quantification do not include Reference standards.
- For the quantification of MPL, DOPC, and Cholesterol, the company uses reference standards from commercial sources that provide Certificates of Analysis (CoA).
- For quantification of QS-21, an in-house produced reference standard is used.
- Qualification of a new reference standard always requires that the proposed new reference standard complies with the QC release specifications.
- For MPL, QS-21, DOPC, and Cholesterol reference standards, the (b) (4)
- The equivalence between QC testing results obtained with the proposed standard versus QC testing results obtained with current (b) (4) analytical sessions.

Reviewer: The justification of specifications is acceptable.

2.5.7 AS01B Container Closure System and Study of (b) (4) of Stoppers

From 3.2.P.7 Container Closure system

- The liquid formulation is filled in 3 ml vial containers, sealed with (b) (4) stoppers for liquid formulations and secured with flip-off caps. Vial containers, vial stoppers and vial flip-off caps are received separately and their assembly is carried out during the filling and packaging operations.
- The 3 ml vial containers are made of type (b) uncolored glass, are sterilized by (b) (4), meet (b) (4) requirements for (b) (4) in compliance with (b) (4). Tests, acceptance criteria, and methods are reported in the GSK (b) (4)
- The (b) (4) vial stoppers are made of (b) (4) type (b) rubber, are supplied by (b) (4) and are sterilized by (b) (4). A letter of authorization to reference (b) (4) (b) (4) is provided in 3.2.R Regional Information. The stoppers meet (b) (4) . The stoppers are (b) (4) with (b) (4) in compliance with Ph. Eur. requirements.
- The vial flip-off caps are made of colored (b) (4) top fixed on a natural (b) (4) cap that are not sterilized.

The bulk of information on Container Closure System for AS01B FC 3 mL vials is provided in 3.2.P.2.4 and is summarized below.

The suitability of 3 mL containers was evaluated by testing compatibility, protection/integrity and safety.

COMPATIBILITY

Compatibility between AS01 Adjuvant System and primary container/closure material is demonstrated through long-term stability studies.

PROTECTION

- *Protection from light.* The protection from light requirement is fulfilled by the opaque secondary packaging component.
- *Container closure integrity.* The container closure integrity test was carried out at different time points to demonstrate that the container closure system maintains its integrity during storage of the vaccine. This test consists of several (b) (4) steps applied to the samples (b) (4)

STUDY OF (b) (4) (SAFETY EVALUATION)

The study was performed on stoppers only as vials are made of type (b) glass.

(b) (4)

The evaluation of (b) (4) on stoppers was performed using (b) (4) . The following tests were employed:

- (b) (4)

(see Table 24 below)

Table 24 (b) (4)

(b) (4)				

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

(b) (4)

2.5.8 AS01B Manufacturing Process Development

- AS01B Adjuvant is part of the AS01 family of Adjuvant Systems that has other variants. The most closely related is the AS01E Adjuvant that contains half the amounts of constituents of the AS01B Adjuvant. AS01E adjuvant is part of the GSK's malaria vaccine, Mosquirix. The development of AS01B was initiated before that of AS01E and the two variants share the same intermediates (b) (4)
- The manufacturing process of AS01B Adjuvant has been developed through the use of (b) (4) where changes in the manufacturing of (b) (4) and AS01 formulation were introduced.
- The term "Industrialization" refers to the facilities used to produce AS01B FC GMP lots during product development. The development of the manufacturing process of AS01B Adjuvant System was initiated at GSK's Pilot Plant and was transferred to Industrialization facilities. (b) (4) were produced in the Pilot Plant; (b) (4) and following (b) (4) were produced in the Industrialization facility. gE/AS01B Phase III studies have been performed with AS01B (b) (4) FC lots.
- After that, the manufacturing process was transferred from Industrialization to commercial facilities for the production of (b) (4) commercial consistency campaigns (b) (4) These facilities will also be used for subsequent routine commercial campaigns. In commercial facilities, the AS01 formulation step was scaled-up to meet the commercial needs.
- In the section "AS01B Formulation development (P.2.21)", the sponsor described that initially, non-clinical immunogenicity and toxicology studies were performed with (b) (4) Later, gE antigen was combined with AS01B for the Phase II clinical trials. Based on the first clinical evaluation of suitable antigen and adjuvant dosage, the combination gE/AS01B was used in a Phase III efficacy study. Throughout clinical evaluation, the AS01B Adjuvant System was presented in single-dose 3 mL glass vials. Table 25 below (Table 1 from P.2.2.1, formulation development) shows lots of AS01B used in pivotal clinical studies.

Table 25 AS01B Adjuvant lots used in Zoster pivotal clinical studies

AS01B Final Container Lots	**Manufacturing facility***	**Usage**
DAS01B009A2	Pilot plant	Phase I/II study: Explo-CRD-004
DA1BA003A	Pilot plant	Phase II study: Zoster-003
DA01A005A	Industrialization	Phase I/II studies: Zoster-001, Zoster-010 and Zoster-023
DA01A023A	Industrialization	Phase III efficacy studies: Zoster-006 & Zoster-022
DA01A027A	Industrialization	Phase III efficacy studies: Zoster-006 & Zoster-022
DA01A029A	Industrialization	Phase III efficacy studies: Zoster-006 & Zoster-022

AS01B Final Container Lots	Manufacturing facility*	Usage
DA01A031A	Industrialization	Phase III efficacy studies: Zoster-006 & Zoster-022
DA01A031B	Industrialization	Phase III efficacy studies: Zoster-006 & Zoster-022
DA01A032A	Industrialization	Phase III efficacy studies: Zoster-006 & Zoster-022
DA01A050A	Industrialization	Phase III efficacy studies: Zoster-026, Zoster-032, Zoster-033
DA01A052A	Industrialization	On-going Phase III efficacy studies
DA01A055A	Industrialization	Phase III efficacy studies: Zoster-004
DA01A055B	Industrialization	On-going Phase III efficacy studies
DA01A056A	Industrialization	Phase III consistency studies: Zoster-007
DA01A058A	Industrialization	Phase III consistency studies: Zoster-007
DA01A059B	Industrialization	Phase III consistency studies: Zoster-007

* Industrialization refers to (b) (4) facilities. Industrialization lots are GMP development lots produced for clinical trials.

Brief description of the changes in the AS01B formulation during clinical development (3.2.P.2.3)

Change in the (b) (4) *during clinical development*:

- The most significant change in the formulation of AS01 Adjuvant System during clinical development was the change in the (b) (4) used in formulation of AS01B Adjuvant.
- (b) (4)

:

(b) (4)

2.5.9 AS01B Formulation Process Performance Qualification: Consistency of the Manufacturing and Validations of (b) (4)

Comparability between industrialization and commercial processes and consistency of the manufacturing

Comparability and consistency data were generated on each (b) (4)

(b) (4) Process Performance Qualification lots (PPQ lots) of AS01B were formulated in (b) (4) facility and were filled in (b) (4) facility (b) (4) campaign) in November 2014, lots (b) (4) of vials were rejected after visual inspection.

Table 26 List of tests that were performed to determine comparability and consistency of manufacturing

Category	Production Step tested	Output	Type of test
Tests performed during the Formulation process	(b) (4)		
Tests performed during the Filling Process			
End process tests Formulation and Filling			

Category	Production Step tested	Output	Type of test
	(b) (4)		
End process tests Filling			

For comparability assessment, historical data from the GMP reference batches that were manufactured in (b) (4) Industrialization facilities in 2007-2012 (b) (4)) were used. Statistical analysis (b) (4) .

For some of the tests performed during the formulation process on the (b) (4) PPQ batches, no data were available on the reference batches for comparison. For instance, no (b) (4) step was applied to the reference batches and therefore, (b) (4) was compared before and after (b) (4) .

- (b) (4)

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

(b) (4)

2.5.10 AS01B Final Container Stability and In-Use Stability of the gE/AS01B Reconstituted Vaccine

The sponsor performed multiple stability studies of AS01B FC using AS01B lots from (b) (4) The list of stability studies is provided in Table 1 in 3.2.P.8.1 and described below.

The following AS01B FC lots were used in the long-term, (b) (4) stability studies:

Long-term stability studies

- (b) (4)

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

(b) (4)

Conclusion, shelf life

- Based on the available stability data generated on AS01B clinical development lots and the comparability of the commercial lots to these reference lots, the Company proposes a shelf-life of 36 months at +2°C to +8°C for AS01B Adjuvant System filled in 3 mL glass vials. In addition, the AS01B Adjuvant System may sustain exposure to (b) (4)

Reviewer: The current recommendation for a 36-month shelf-life for AS01B stored at 2 to 8°C is acceptable

In-Use Stability of gE/AS01B Reconstituted Vaccine

Several types of stability studies were performed in relation to stability of SHINGRIX and its components: stability of the gE FC lots (Reviewed by antigen reviewer, Dr. Shuang Tang), of the AS01B FC lots and stability of the gE/AS01B Reconstituted Vaccine (RV) (all described in P.8 of the gE DP dossier).

Reviewer: It is important to note, that in the studies where gE is/was reconstituted with AS01B, in addition to pH of the solution, only gE-related attributes were evaluated (gE content by ELISA and gE (b) (4) **None of the studies described in 3.2.P.8 (gE dossier) including the in-use stability, evaluate physicochemical properties of adjuvant component. Below I list on-going stability studies performed on gE FC with and without reconstitution with AS01B and a brief summary of the in-use stability of the gE FC reconstituted with AS01B adjuvant.**

On-going stability studies of gE FC:

- (b) (4)

For gE FC alone, the following parameters were tested during stability evaluation:

- (b) (4)

For gE reconstituted with AS01B, the following parameters were tested during stability evaluation:

- (b) (4)

(b) (4)

Based on these data, the sponsor issued the following recommendation regarding maximum duration of time for storage of reconstituted vaccine: "to avoid potential contamination and to preserve the sterility of the final reconstituted vaccine, the vaccine must be used promptly after reconstitution. If this is not possible, the reconstituted vaccine should be stored in a refrigerator (2°C to 8°C) and used within a maximum of 6 hours. If not used within 6 hours, the reconstituted vaccine should not be administered."

Reviewer: In the short-term stability studies of the reconstituted vaccine, the sponsor evaluated pH and two characteristics of the gE antigen: total content by ELISA and (b) (4) . None of the attributes specific to AS01B adjuvant were assayed. However, (b) (4) showed that the levels of antibody response to gE antigen were not affected by (b) (4) storage of the vaccine suggesting that none of the physicochemical qualities of adjuvant were affected by the storage. Also, even though data were provided for a minimum of (b) (4) of storage, the sponsor used a conservative approach and recommended a maximum of 6 h storage of the reconstituted vaccine before administration as described in Administration Instructions in 1.14.1.3 (Labeling, Module 1). These recommendations are acceptable.

2.5.11 AS01B Certificate of Analysis

- Certificates of Analysis are provided for the following batches of AS01B Final Bulk and AS01B Final Container (all in 3.2.R Regional Information)
    - Final Bulk: (b) (4)
    - Final Container: (b) (4)
- All parameters are within specification

2.5.12 gE/AS01B Compatibility

The objective of the compatibility assessment between the gE DP and AS01B adjuvant was to demonstrate

a. The absence of interactions between the gE and AS01B and absence of interactions with the container
b. The interchangeability of vaccine components.

The compatibility of the gE and the AS01B Adjuvant System with the final container is confirmed by stability and clinical data.

Antigen-adjuvant interactions

The potential for physicochemical interaction or binding between the gE antigen and the AS01B Adjuvant System was studied on the gE/AS01B final reconstituted vaccine (RV). Clinical consistency lots, clinical efficacy lots, and commercial lots were tested. These studies are described in Section 3.2.P.2.6 Compatibility Ag-AS01B Interaction gE/AS01B RV (gE DP dossier).

For each study, (b) (4) independent pairs of gE and AS01B FC lots were tested directly after extemporaneous reconstitution or after (b) (4) After reconstitution, the components of the vaccine were (b) (4) This indicates the absence of physicochemical interaction or binding between these two moieties.

Interchangeability

The interchangeability was demonstrated through testing of (b) (4) gE/AS01B reconstituted vaccine combinations (b) (4) independent gE Final Container commercial lots each combined with each of the (b) (4) AS01B commercial lots] and statistical analysis of the results. The following tests were performed after extemporaneous reconstitution of gE FC with AS01B FC: (b) (4)

Results:

- Results for all (b) (4) gE/AS01B RV combinations were within the acceptance criteria.
- (b) (4)

Compatibility with final container

Stability studies support the compatibility of gE and of AS01B with their respective container closure components and support the compatibility between the AS01B Adjuvant System and the lyophilized gE antigen for which it serves as diluent. The compatibility is further validated by clinical evaluation of HZ/su vaccine.

2.5.13 AS01B DP Control of Excipients, MPL

Compendial materials

The following compendial materials are used: Sodium chloride, Disodium phosphate anhydrous, Water for injections, MPL.

- (b) (4)

AS01B DP Excipients of Human or Animal Origin

- With the exception of (b) (4) that are used during the production of MPL, no materials from human or animal origin are used in the manufacture of the AS01 Adjuvant.
- (b) (4)

Novel excipients

The following novel excipients are used in the manufacture of AS01 Adjuvant Systems: (b) (4) cholesterol and (b) (4) (b) (4) QS-21 and DOPC.

The production of all three novel excipients is described in detail including manufacture, analytical procedures, and method validation. Below, I provide summaries of manufacture of each novel excipient: cholesterol, QS-21, and DOPC.

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