



REVIEW MEMORANDUM

To: Robin Levis, Ph.D., DVP, OVRR, CBER, FDA

From: Elizabeth M. Sutkowski, Ph.D., DVRPA, OVRR, CBER, FDA

Through: Paul G. Richman, Ph.D., DVRPA, OVRR, CBER, FDA

Subject: STN 125259: BLA from GSK (Glaxo Group Ltd., d/b/a GlaxoSmithKline) for Human Papillomavirus Vaccine, AS04 Adjuvant-Adsorbed: Review of the Chemistry, Manufacturing and Control Information Relevant to 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) and AS04 Adjuvant System

Cross- reference(s): IND -(b)(4)-
IND -(b)(4)-

TABLE OF CONTENTS

FDA Reviewer’s Overall Summary and Conclusion.....	Page	3
Listing of Submissions Reviewed Herein	Page	7
List of Abbreviations.....	Page	9
I. Introduction.....	Page	10
II. Overview of Manufacture.....	Page	12
III. Drug Product: Information Regarding MPL-Containing Intermediates and AS04 Adjuvant System in the HPV Vaccine.....	Page	15
IV. AS04 Adjuvant Component: MPL -----(b)(4)-----	Page	59
V. References.....	Page	103

Lipopolysaccharide (LPS) is obtained by extracting *S. minnesota* R595 ----(b)(4)----

The critical parameters for the production of the MPL -(b)(4)- and MPL-containing intermediates were validated according to defined validation criteria and presented in the BLA. The consistency and robustness of the MPL production process is demonstrated through analyses of the process data collected during the manufacture of -----(b)(4)-----

----- (b)(4) ----- as well as through the analysis of Quality Control data for the release of MPL --(b)(4)--.

The manufacturing process for MPL -(b)(4)-, MPL-containing intermediates, and HPV Vaccine has been --(b)(4)-- in several stages during development, and data were submitted that demonstrate that batches manufactured according to revised processes have comparable physico-chemical and immunological properties. With respect to the MPL --(b)(4)--, the --- (b)(4) --- of the ----- (b)(4) ----- was described in detail in the Class 2 Resubmission to the BLA (in Serial 48). ***A new comparability protocol was provided in Serial 48 to the BLA that included 1) a description of the changes in the process for preparation of the MPL - (b)(4) ----- at the ----- (b)(4) ----- scale; 2) a description of the plan for demonstrating comparability between the ----- (b)(4) ----- for MPL --- (b)(4) --- batches; and 3) acceptance criteria for the implementation of the ----- (b)(4) ----- scale.*** Also, comparability data supporting the change, which demonstrate that the MPL --- (b)(4) --- prepared using the ----- (b)(4) ----- process meets the acceptance criteria, are provided in the BLA. In addition, the available stability data show that MPL ---- (b)(4) --- batches prepared using the ----- (b)(4) ----- process are stable at ----- (b)(4) ----- as demonstrated by the fact that all stability-indicating parameters remained similar to the initial values over the --- (b)(4) --- period. ***The firm may need to be informed that we acknowledge receipt (in the Resubmission) of the data submitted to support their comparability protocol titled, “Comparability Protocol for the Preparation of MPL -(b)(4) - Produced Via the ----- (b)(4) -----,” and we approve this comparability protocol. Also, we accept their proposal to have a shelf life of ----- (b)(4) ----- for the MPL --- (b)(4) --- batches prepared using the ----- (b)(4) ----- scale process. In addition, we would expect them to provide complete, long term, real-time stability data from studies of the MPL --- (b)(4) --- prepared using the ----- (b)(4) ----- scale process to support an extension of the shelf-life beyond ----- (b)(4) ----- for MPL --- (b)(4) --- prepared using the ----- (b)(4) ----- scale process.***

In addition, it was noted in the Resubmission to the BLA (Serial 48) that MPL --- (b)(4) --- is to be ---- (b)(4) --- in an ----- (b)(4) -----, which is anticipated to be functionally equivalent based on the fact that it has almost identical characteristics and routine container closure materials. Thus, the firm anticipates that the --(b)(4)-- will provide the same level of product protection and have no impact on MPL quality or stability. ***Development and validation studies have demonstrated that use of the proposed ----- (b)(4) ----- does not adversely impact the validated MPL ----- (b)(4) ----- cycle or the quality of MPL -(b)(4)-. In addition, the proposed ----- (b)(4) ----- is anticipated to have no impact on MPL stability, which will be confirmed by ongoing and future stability testing.*** Available stability data (from ----- (b)(4) -----) were provided for -(b)(4)- of MPL ---- (b)(4) --- in the proposed ----- (b)(4) ----- presentations. ***GSK stated their plans to collect stability data for subsequent time-points and provided these data in future Annual Reports to the BLA. The continued submission of these data may need to be a PMC: You have committed to providing complete, long term, real-time stability studies of the MPL (----- (b)(4) -----) in the proposed ----- (b)(4) -----.***

presentations at ---(b)(4)--- to provide confirmation that that the -----(b)(4)----- does not adversely impact MPL stability.

In addition, we may want to recommend that the firm try to tighten the specifications for the -(b)(4)-MPL -(b)(4)-, MPL --(b)(4)--, and MPL adsorbed bulk as they gain more experience manufacturing these components for use in the AS04-adjuvanted HPV Vaccine.

All CMC items in the CR letter regarding MPL -(b)(4)- and AS04 adjuvant system in the final drug product (i.e., items 16 through 20) were addressed in Serial 30 (received 28-FEB-2008), and the responses were reviewed and found to be complete and adequate. In response to item 20 regarding the testing and acceptance criteria for new *S. minnesota* R595 Working Seeds, the firm submitted an acceptable comparability protocol (CP) titled “Comparability Protocol for Qualification of *S. minnesota* R595 Working Seed Lots.” In addition, ***GSK proposed that all new WS lots qualified according to this CP be reported via Annual Reports to the BLA. As this is an acceptable approach, we may want to inform GSK of the following: We have approved your comparability protocol titled “Comparability Protocol for Qualification of *S. minnesota* R595 working Seed Lots.”***

Finally, in the Resubmission (Serial 48), the firm reports that many of the reference standards instrumental in testing of key aspects of the drug product will run out during 1Q/2Q2009. To avoid any impact this may have on the production of launch supplies, GSK validated new standards for use in the manufacturing process. Each standard was tested, as per the available validation protocols, and results compared to current validity criteria. All of the results complied with the acceptance criteria. This included the replacement of the current MPL ----(b)(4)--- ----- Reference Standard, established for the testing of the MPL content by -(b)(4)- test of HPV Final Container, with the MPL ----- (b)(4)----- Reference Standard (implemented in March 2009). This reference standard is a routine preparation of MPL -(b)(4)- -----.

Regarding the Stability Protocols, the analytical methods used are the same as the Quality Control and characterization methods used for the testing of MPL -(b)(4)-, MPL ----(b)(4)---, and MPL Adsorbed Bulk, and AS04 adjuvant system in the final adjuvanted HPV Vaccine, as appropriate. Based on real-time stability data, the Company proposes the following:

1. -----(b)(4)-----
2. -----(b)(4)-----
-----.
3. -----(b)(4)-----
4. A shelf life of 36 months for the HPV vaccine, in syringes and vials, when stored at +2°C to +8°C.

Conclusion and Recommendation:

In summary, the CMC information and data relevant to the MPL -(b)(4)-, MPL ----(b)(4)---, MPL adsorbed bulk, and AS04 adjuvant system in the HPV-16/18 L1 VLP AS04 Vaccine that have been presented in this BLA are complete and adequate to demonstrate that the AS04 adjuvanted HPV Vaccine is manufactured under cGMP by a validated process and the AS04 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 MPL- and AS04-relevant CMC information presented in the Quality module of the BLA support the approval of the BLA for manufacture of the HPV-16/18 L1 VLP AS04 Vaccine. I recommend approval of the BLA for GSK's HPV-16/18 L1 VLP AS04 vaccine.

Listing of Submissions Reviewed Herein:

The CMC information and data related to the Drug Substances (HPV-16 L1 VLP and HPV-18 L1 VLP antigens) and the Drug Product (HPV-16/18 L1 VLP AS04) have been reviewed by Dr. Robin Levis in a separate document.

The CMC information and data reviewed in this document include data on the manufacture, characterization, quality control and stability of 1) the MPL -(b)(4)- (as presented in Module 3, Appendix 3.2.A.3. Novel Excipients and Module 3.2.P.4e Control of Excipients); 2) the Drug Product Intermediates: MPL ----(b)(4)----, MPL Adsorbed Bulk (presented in Module 3.2.P. Drug Product and Module 3.2.P.4e Control of Excipients); and 3) the AS04 adjuvant system in the final drug product, HPV-16/18 L1 VLP AS04 vaccine (also presented in Module 3.2.P. Drug Product). In addition, the summary of all of the above data (provided in Module 2.3. Quality Overall Summary) was reviewed.

An itemized list of sections of the original submission to the BLA (BLA OA) and Amendments to the BLA OA that are reviewed in this CMC review follows.

Type/Application ID/Amendment #/Receipt Date:

Biologic License Application (BLA)/STN 125259/Original Application (Am. 0)/29-MAR-2007:

- Quality Overall Summary Module 2.3
- CMC information and data on the manufacture, characterization, quality control and stability of the MPL -(b)(4)- as presented in Module 3, Appendix 3.2.A.3. Novel Excipients
- CMC information and data on the two MPL-containing HPV Vaccine production intermediates: the MPL ----(b)(4)---- and MPL Adsorbed Bulk as presented in the Vaccine Drug Product Section in Module 3.2.P.1 Description and composition of the Drug Product, 3.2.P.3 Description of Manufacturing Process and Process controls, and Module 3.2.P.4. Control of Excipients
- CMC information and data regarding MPL in the Vaccine Drug Product as presented in Module 3.2.P.1 Description and composition of the Drug Product; 3.2.P.3 Description of Manufacturing Process and Process controls and Module 3.2.P.4. Control of Excipients
- CMC information and data regarding MPL as presented in the Quality Section 3.2.R Regional Information regarding the Batch Records, Analytical Procedures, Validation of Analytical Procedures, Draft Release Protocols, Certificates of Analysis, and Comparability Protocol for -----(b)(4)-----

Amendment to BLA/STN 125259/Seq. 20/19-OCT-2007:

CMC responses to FDA's request for information received by GSK via email on October 1, 2007 regarding -(b)(4)- of MPL --(b)(4)--, MPL ---(b)(4)----, and MPL adsorbed bulk

Amendment to BLA/STN 125259/Seq. 25/21-NOV-2007:

Response to Question 8 of communication sent to GSK on 10/1/07 regarding inaccuracies in the CMC information in the BLA

Amendment to BLA/STN 125259/Seq. 30/28-FEB-2008:

Response to items 16 - 20 (regarding MPL -(b)(4)- and AS04 Adjuvant System) in FDA's Complete Review Letter dated December 14, 2007

Amendment to BLA/STN 125259/Seq. 42/29-AUG-2008:

Proposed Changes for Class 2 Resubmission (Post FDA Review of BLA Quality Section):
RE MPL these changes include e.g., -----(b)(4)----- of MPL ---(b)(4)--- from --(b)(4)--, proposal for new -----(b)(4)----- for MPL -(b)(4)-, etc.

Amendment to BLA/STN 125259/Serial 47/19-DEC-2008:

1) Response to FDA's November 5, 2008 Cervarix - CMC comments e-mail and 2) additional BLA CMC amendment information package with information on -----(b)(4)----- for MPL ---(b)(4)--

Amendment to BLA/STN 125259/Serial 48/27-MAR-2009:

Class 2 Resubmission and Request to Re-Start Review Clock with changes to manufacture of MPL: -----(b)(4)----- of MPL ----(b)(4)--- from ----(b)(4)---; Qualification of new Reference Standard for MPL ----(b)(4)---

Amendment to BLA/STN 125259/Serial 63/7-AUG-2009:

Submission of the revised DRAFT *Cervarix* Lot Release Protocol (m1.11.1)

Amendment to BLA/STN 125259/Serial 74/28-SEP-2009:

Response to FDA's request for information emailed on 9-25-09: Submission of stability data for MPL ---(b)(4)--- prepared at the -----(b)(4)----- through -----(b)(4)-----

List of Abbreviations

BLA	Biologics license application
GSK	Glaxo Group Ltd., d/b/a GlaxoSmithKline
HPV	Human papillomavirus
VLP	Virus-like particle
MPL	3- <i>O</i> -desacyl-4'-monophosphoryl lipid
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
-(b)(4)-	----- (b)(4) -----
Al(OH) ₃	Aluminum hydroxide
L1	Major capsid protein of HPV
AMB	Adsorbed Monovalent Bulk(s)
-(b)(4)-	----- (b)(4) -----
LPS	Lipopolysaccharides
FFA	free fatty acids
-(b)(4)-	----- (b)(4) -----

I. INTRODUCTION

GSK's HPV-16/18 L1 VLP AS04 vaccine is an adjuvanted, recombinant preservative-free vaccine turbid liquid suspension for intramuscular injection. The HPV-16 L1 and HPV-18 L1 proteins constitute the active ingredient of the vaccine and are produced with a recombinant Baculovirus expression system. The vaccine adjuvant system, AS04, consists of aluminum hydroxide-adsorbed 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL). The MPL component, which is considered by GSK to be an immunostimulant, is a detoxified derivative of the lipopolysaccharides (LPS) of the gram negative bacterium *Salmonella minnesota* R595 strain. MPL --b(4)-- is manufactured and supplied by Corixa Corporation, doing business as GSK Biologicals North America, Hamilton, Montana, USA. The AS04 adjuvanted HPV Vaccine is manufactured by: GlaxoSmithKline Biologicals, Rue de l'Institut, 89, B-1330 Rixensart, Belgium.

It is stated by GSK that the HPV vaccine composition was determined based on the data obtained from nonclinical challenge animal models and from clinical epidemiological and natural history studies, which showed that in order to be efficacious in preventing HPV infection and related clinical lesions an HPV vaccine would need to induce strong antibody responses against the L1 capsid protein (assembled as VLPs), B-cell memory and T-cell responses. The HPV vaccine formulation was therefore selected to be a combination of L1 proteins assembled as VLPs, to insure the induction of protective anti-HPV L1 VLP antibodies, and the proprietary adjuvant AS04 developed by GSK Biologicals, to insure the induction of sustained high levels of antibodies as well as the induction of a specific cell-mediated immunity [Garcon, 2006; Giannini et al, 2006].

This is a review of the Chemistry, Manufacturing and Control (CMC) information regarding the one of the starting materials (MPL ---b(4)--) and the AS04 adjuvant included in the BLA STN 125259 from GSK (Glaxo Group Ltd., d/b/a GlaxoSmithKline) for Human Papillomavirus Vaccine, AS04 Adjuvant-Adsorbed, as titled in RMSBLA. Throughout this review, the HPV-16/18 L1 VLP AS04 vaccine will be referred to as the HPV vaccine (or the adjuvanted HPV vaccine or Cervarix) and rather than referring to the AS04 adjuvant or MPL as an excipient (as GSK does throughout the BLA), it will be referred to as an adjuvant or an additive.

The tables and figures in this review are GSK's tables and figures; they were copied from various parts of the BLA and renumbered in this review.

I.A. Components of the Drug Product

I.A.1. Drug Substance

Recombinant C-terminally truncated L1 proteins from Human Papilloma Virus type-16 and type-18 (HPV-16 and HPV-18) each assembled as virus-like particles (VLP) constitute the two active drug substances of GSK Biologicals' HPV vaccine.

The HPV-16 L1 VLP and HPV-18 L1 VLP antigens are prepared using a novel technology based on the use of -----(b)(4)----- cells and HPV-16 and HPV-18 recombinant Baculoviruses. Using this expression system, the highly purified L1 VLP antigens are obtained through infection of the -----(b)(4)----- cell line with the recombinant Baculoviruses followed by extensive purification.

The CMC information and data provided in the BLA for these two drug substances and the HPV Vaccine was reviewed in a separate document by Robin Levis, Ph.D.

I.A.2. Drug Product Intermediates

The MPL-containing Drug Product Intermediates include -----(b)(4)-----
----- . The CMC information for these intermediates is reviewed under Section III of this review.

I.A.3. Additives

The following five additives (which GSK refers to as excipients) are contained in the HPV vaccine:

- Aluminum hydroxide: $\text{Al}(\text{OH})_3$ is present in the finished product as part of the AS04 adjuvant system. $\text{Al}(\text{OH})_3$ is present at 500 mcg / dose.
- 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL): MPL is present in the finished product as part of the AS04 adjuvant system. MPL is present at 50 mcg/dose. The chemistry, manufacture, and control (CMC) information for MPL -(b)(4)- (the starting material for MPL -(b)(4)- bulk) is reviewed in Section IV of this BLA.
- Sodium chloride: Sodium chloride is present in the finished product to ensure isotonicity. It is present at 150 mM or 4.4 mg/dose.
- Sodium dihydrogen phosphate dehydrate $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ is present in the finished product to -----(b)(4)----- . It is present at 8 mM or 0.624 mg/dose.
- Water for injection: Sterile water for injections is used as solvent for the parenteral HPV vaccine.

(b)(4)

----- (b)(4) -----

(b)(4)

----- (b)(4) -----

(b)(4)

The final container HPV vaccine results from the aseptic filling of the final bulk -----(b)(4)-----
----- into ---(b)(4)--- sterile syringes (type -(b)(4)- glass) or into 3 ml colorless -(b)(4)-
sterile glass vials (type -(b)(4)-) by an automatic filling/stoppering machine. After filling, the
syringes or the vials are automatically closed with grey -(b)(4)-- stoppers. Vials are then capped
with flip-off caps.

The vaccine should be stored at +2°/+8°C (in a refrigerator). The proposed shelf life is 3 years. The vaccine should not be frozen.

Production of the HPV vaccine is carried out in aseptic conditions (class -(b)(4)- – grade -(b)(4)-), except for the preparation of sterile -(b)(4)-, which is performed in a non-aseptic classified room (class -(b)(4)-) but with the final sterilizing filtration taking place in an aseptic room (class -(b)(4)-grade -(b)(4)-).

The composition of the HPV Vaccine is given in Table 1.

Table 1 Composition of the HPV Vaccine

Ingredients	Quantity (per 0.5ml dose)
HPV-16 L1 VLP	20 mcg
HPV-18 L1 VLP	20 mcg
MPL	50 mcg
Aluminum (hydroxide salt)	500 mcg
Sodium chloride (NaCl)	4.4 mg (150 mM)
Sodium dihydrogen phosphate dihydrate (NaH ₂ PO ₄ ·2H ₂ O)	0.624 mg (8 mM)
Water for injection	q.s. ad 0.5 ml

The vaccine is a preservative-free product available as a 0.5 mL single-dose in 3 mL glass vials (fill volume = -(b)(4)-) and as a 0.5 mL single-dose in pre-filled, TIP-LOK® disposable 1.25 mL glass syringes (fill volume = -(b)(4)-).

The HPV vaccine is manufactured under current Good Manufacturing Practices (cGMP) [per 21 CFR Part 211]. Many precautions are taken during the preparation of the HPV vaccine to ensure the sterility of the final product.

- The manufacture of the active ingredients is carried out in conditions that ensure that the antigen purified bulks are sterile. To ensure the sterility of the purified antigens, the -----(b)(4)----- entering the vaccine composition are sterile filtered and tested for sterility according to -----(b)(4)----- and 21 CFR requirements.

Page 14 – Review of MPL-Relevant CMC Information in Cervarix BLA (STN 125259)

One (1) page determined to be non-releasable: (b)(4)

III. DRUG PRODUCT

Note - Areas below that are bolded indicate that changes have been made since the original application. The bolded item is taken from the most current version of the information, provided in Serial 48.

III.A. Manufacturer(s)

The manufacture of the HPV-16/18 L1 VLP AS04 vaccine, filling, labeling and packaging and QC testing are performed by GlaxoSmithKline Biologicals S.A, Belgium according to Good Manufacturing Practices.

The formulation and filling of the vaccine are performed at the Rue de l'Institut 89, 1330 Rixensart and Parc de la Noire Epine, Rue Fleming 20, 1300 Wavre, Belgium.

The labeling and packaging operations are performed at the Parc de la Noire Epine, Rue Fleming 20, 1300 Wavre, Belgium

QC testing and release of the HPV vaccine drug product is performed at Parc de la Noire Epine, Rue Fleming 20, 1300 Wavre, Belgium. Animal testing (such as general safety test) is performed at Rue de l'Institut, 89, 1330 Rixensart, Belgium.

III.B. Description of Manufacturing Process and Process Controls

The manufacture of the HPV-16/18 L1 VLP AS04 vaccine consists of the following steps:

----- (b)(4) -----

----- (b)(4) -----

The flow sheets for each manufacturing step along with the identification of the process or quality control testing are presented in the sections below.

Page 16 – Review of MPL-Relevant CMC Information in Cervarix BLA (STN 125259)

Two (2) pages found to be non-releasable: (b)(4)

-(b)(4)-----

[
--(b)(4)--
]

FDA Reviewer's Note:

The preparation of MPL ----- (b)(4) ----- step. As communicated to the Agency during the pre-BLA meeting on May 1, 2006, GSK Bio had plans to -(b)(4)- the ----- (b)(4) ----- . Based on the Agency's comments received during the pre-BLA meeting, this proposed change to the MPL ----- (b)(4) ----- would require the submission of a prior approval supplement. However, due to the anticipated market demand, GSK Bio submitted a comparability protocol in Serial 48 to the BLA to provide a detailed description of the ----- (b)(4) ----- change. Therefore, the present comparability protocol, which replaces the comparability protocol initially submitted in the BLA, has been revised in order to include the parameters corresponding to the proposed -(b)(4)- ----- . As discussed in GSK's August 29, 2008 General Correspondence: CMC, Other - Request for FDA Review and Response: Proposed CMC Changes Post FDA Review of BLA Quality Section, the data to support this change is available and is being submitted in parallel with the present Comparability Protocol and the appropriate CTD sections have been revised. Therefore, a separate CBE-30 supplement will not be filed after BLA approval for this change.

This comparability protocol includes:

- Description of the changes in the process for preparation of the MPL -(b)(4)-----
-----;
- Description of plan for demonstration of the comparability between the -(b)(4)-----
----- for MPL -----(b)(4)-----; and
- Acceptance criteria for the implementation of the -----(b)(4)-----

The manufacturing change and the comparability data to support the change are summarized below:

------(b)(4)-----

------(b)(4)-----

------(b)(4)-----

------(b)(4)-----

------(b)(4)-----

------(b)(4)-----

------(b)(4)-----

Page 19 – Review of MPL-Relevant CMC Information in Cervarix BLA (STN 125259)

Seven (7) pages determined to be non-releasable: (b)(4)

-(b)(4)-----

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--(b)(4)--
]

The tests to be conducted to release HPV vaccine final bulk (as part of the Formal Lot Release Testing Protocol, submitted in Serial 63) are reproduced below:

Tests on final bulk, Lot No. :

STERILITY TEST

Method used (b)(4)

On test date	Medium	Tested Quantity	Temperature	Off test date
	Fluid thioglycollate	10 ml	30 - 35 °C	
	Soybean casein digest	10 ml	20 - 25 °C	

III.B.5.a. Filling Process

The HPV Vaccine Final Bulk (FB) is aseptically filled under -----(b)(4)----- sterile syringes (Type -(b)(4)-) or into 3 ml colorless -(b)(4)- sterile glass vials (Type -(b)(4)-) via an automatic filling/stoppering machine. After filling, the syringes and vials are automatically sealed with grey --- (b)(4) --- stoppers. Vials are then capped with flip-off caps.

III.B.5.b. Labeling and Packaging Operations

Identified and inspected vaccine final containers (syringes, vials) are placed in boxes, palletized, quarantined and stored at the Warehouse cold rooms (+2 to +8°C) awaiting labeling and packaging.

The filled syringes and vials are labeled automatically on a labeling machine and labeled syringes are thermo sealed in pre-molded plastic trays. The thermo sealed syringes and vials are individually packed, along with a product information insert (leaflet), into a carton box. Lot numbers and expiry dates are printed on each individual box and these are stored in a cold room (+2°C to +8°C) awaiting release and expedition.

The tests to be conducted to release HPV Vaccine Final Container (as part of the Formal Lot Release Testing Protocol, submitted in Serial 63) are reproduced below:

Tests on final container, Lot No. :

Tests	Specification	Date of results	Results
DESCRIPTION	Turbid liquid after shaking; white deposit and colorless supernatant after sedimentation		Pass
(b)(4)	(b)(4)		
VOLUME			ml
MPL CONTENT by (b)(4) (b)(4)			µg/ml
(b)(4)			%

STERILITY TEST

Method used (b)(4)

On test date	Medium	Tested Quantity	Temperature	Specification	Off test date
	Fluid thioglycollate	20 containers	30 - 35 °C	Absence of growth	
	Soybean casein digest	20 containers	20 - 25 °C	Absence of growth	

ABNORMAL TOXICITY - GENERAL SAFETY

Specification: All the animals survive the observation period, none of them show weight loss, and none exhibit an unexpected response suggesting change in product quality.

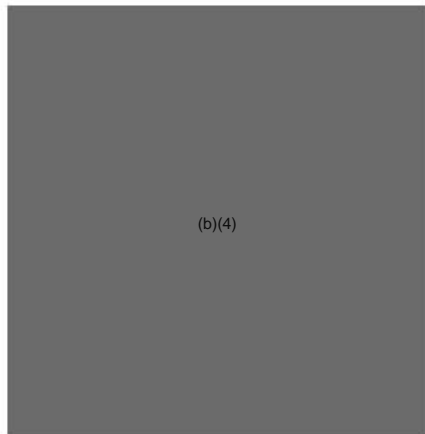
On test date	Animal species	Animal No	Route of inoc.	Volume of inoc.	Initial weight	Final weight	Off test date	Result
	Mouse		i.p.	0.5 ml	g	g		Pass
	Mouse		i.p.	0.5 ml	g	g		Pass
	Mouse		i.p.	0.5 ml	g	g		Pass
	Mouse		i.p.	0.5 ml	g	g		Pass
	Mouse		i.p.	0.5 ml	g	g		Pass
	Guinea Pig		i.p.	5.0 ml	g	g		Pass
	Guinea Pig		i.p.	5.0 ml	g	g		Pass

Tests

ALUMINIUM CONTENT by (b)(4)
(b)(4) method

Specification	Date of results	Results
(b)(4)		mg/dose

Tests



Specification	Date of results	Results
(b)(4)		µg/dose
		%
		%

Tests

IDENTITY HPV-16 L1 VLP by

(b)(4)

IDENTITY HPV-18 L1 VLP by

(b)(4)

Specification	Date of results	Results
(b)(4)		Positive
		Positive

POTENCY HPV-16 L1 VLP by

(b)(4)

POTENCY HPV-18 L1 VLP by

(b)(4)

Specification	Date of results	Results
The relative potency is between (b)(4)		
The relative potency is between (b)(4)		

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

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----- (b)(4) -----

[
--(b)(4)--
]

----- (b)(4) -----

III.C.4. Process Validation and/or Evaluation

Validation of the HPV vaccine production process is performed through the demonstration of process consistency and the identification and validation of the manufacturing process critical parameters.

III.C.4.1. Consistency Demonstration of the HPV Vaccine Production Process

The consistency of the HPV vaccine production process is demonstrated through analyses of the process data collected during the manufacture of the HPV vaccine ----- (b)(4) -----
----- as well as through the analysis of Quality Control data for the release of the HPV vaccine and its ----- (b)(4) -----
-----.

-(b)(4)-----

-(b)(4)-----

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------(b)(4)-----

------(b)(4)-----

[
 --(b)(4)--
]

------(b)(4)-----.

------(b)(4)-----

------(b)(4)-----

Hence, the analysis of Quality Control data and the data collected during preparation of 3 consecutive lots of HPV vaccine (and intermediates) all demonstrate the consistency and robustness of the HPV vaccine production process. Detailed results are presented in **Module 3.2.P.3.5. Process validation and/or evaluation.**

III.C.4.2. Identification and validation of manufacturing process critical parameters

All process variables are categorized into critical or non-critical parameters according to the firm's process validation policy. Critical process parameters are either validated or, alternatively, the performance of the process unit step or module in which these critical parameters operate, are controlled on each produced batch in order to guarantee the unit step or module robustness.

Table 22 summarizes the critical parameters for the production of the HPV vaccine final bulk.

----- (b)(4) -----

[
--(b)(4)--
]

Storage duration has been identified as being a critical parameter for all production steps of the HPV vaccine formulation. These parameters are all followed through stability plans which are detailed in **Module 3.2.P.3.4 Control of Critical steps and Intermediates and Module 3.2.P.8.2 Post approval Stability Protocol and Stability Commitment**. Details of the analytical assays and their validation included in the Stability Plans are presented in **Module 3.2.P.3.4 Control of Critical steps and Intermediates and Module 3.2.P.8.2 Post approval Stability Protocol and Stability Commitment**.

III.C.4.3. Validation of Aseptic Filling

It is stated in the BLA that validation of the vaccine aseptic filling system is run in compliance with the 'Guideline on sterile drug product produced by aseptic processing' (FDA, Sept 2004) and with “Aseptic Processing of Health Care Products – Part 1: General Requirements, Section 21.7.1” (ISO/FDIS 13408-1: 1998). Briefly, the filling validation is performed through three media fill studies. For each of these media fill validation studies, a simulation of the filling operation in syringes or in vials is performed to validate the assurance of sterility for the filling room under evaluation or to demonstrate the capability of the entire aseptic process to produce sterile vaccines in their final containers (see details in **Module 3.2.P.3.5. Process validation and/or evaluation**).

III.C.5. Control of Drug Product

III.C.5.1. Specifications and Methods

----- (b)(4) -----

Table 23 HPV final bulk vaccine quality control tests, specifications and methods

Tests	Specifications	Methods
Sterility test FTM by (b)(4) (at 30-35 °C)	Absence of growth	(b)(4)
Sterility test TSB by (b)(4) (at 20-25 °C)	Absence of growth	

Table 24 HPV final container vaccine quality control tests, specifications and methods

Tests	Specifications	Methods
Description	Turbid liquid after shaking. White deposit and colourless supernatant after sedimentation	Not applicable
Identity HPV-16 L1 VLP by (b)(4)	(b)(4)	In-house
Identity HPV-18 L1 VLP by (b)(4)		In-house
Sterility test FTM by (b)(4) (at 30-35 °C)	Absence of growth	(b)(4)
Sterility test TSB by (b)(4) (at 20-25 °C)	Absence of growth	
General safety - Abnormal toxicity on guinea-pigs	No weight loss , no abnormal reaction	21 CFR
General safety - Abnormal toxicity on mice	No weight loss , no abnormal reaction	(b)(4) 21 CFR
(b)(4)	(b)(4)	(b)(4)
Volume		In-house
(b)(4)		In-house
<i>In vitro</i> potency HPV-16 L1 VLP by (b)(4)		In-house
<i>In vitro</i> potency HPV-18 L1 VLP by (b)(4)		In-house
Aluminium content by (b)(4)		In-house
(b)(4)		In-house
MPL content by (b)(4)		In-house
(b)(4)		In-house
(b)(4)		In-house

IV.C.5.2. Assay Validations

IV.C.5.2.a. Final Bulk

The HPV final bulk is tested for sterility. The sterility tests are performed in compliance with (b)(4)- 21CFR 610.12 and (b)(4)-

IV.C.5.2.b. Final Container

The analytical procedures for the tests listed in Table 25 were performed in compliance with the requirements of -----(b)(4)-----, and/or 21CFR:

Procedures for HPV Final Container performed in compliance with and/or 21CFR Tests Analytical reference

Tests			Analytical reference	
Sterility test FTM by	b(4)	(at 30-35°C)	21CFR610.12,	b(4)
Sterility test TSB by	b(4)	(at 20-25°C)	21CFR610.12,	b(4)
General safety - Abnormal toxicity on guinea-pigs			21CFR610.11	
General safety - Abnormal toxicity on mice			21CFR610.11	
b(4)				
Volume				

The analytical procedures for the in house tests listed in Table 26 were developed in-house.

Table 26 summarizes for each procedure, its category and the parameters that have been validated.

Table 26 Validated QC tests on final container vaccine: test category and validation parameters

In-house tests	Test category	Validation parameters
Identity of the HPV-16 L1 VLP by b(4)	Identification test	Specificity
Identity of the HPV-18 L1 VLP antigen by b(4)	Identification test	Specificity
b(4)	Quantitative test	Dose response curve, linearity, repeatability, intermediate precision, specificity, accuracy.
<i>In vitro</i> relative potency HPV-16 L1 VLP by b(4)	Quantitative test	Accuracy, precision (intermediate and reproducibility), linearity, range, specificity
<i>In vitro</i> relative potency HPV-18 L1 VLP by b(4)	Quantitative test	Accuracy, precision (intermediate and reproducibility), linearity, range, specificity
MPL content by b(4) b(4)	Quantitative test	Linearity, repeatability, intermediate precision, specificity, accuracy
b(4)	Limit test	Detection limit, quantitation limit
	Quantitative test	Dose response curve, range, intermediate precision, specificity, accuracy.
	Quantitative test	Dose response curve, range, intermediate precision, specificity, accuracy.
Aluminium content by b(4) b(4)	Quantitative test	Linearity, repeatability, intermediate precision, specificity, accuracy.

The in house analytical procedures have been validated according to the ICH guidelines Q02A and Q02B.

Details on the validation data for the in-house procedures used for the release of the final container vaccine are provided in **Module 3.2.P.5.3. Validation of Analytical Procedures.**

----- (b)(4) -----

III.C.5.3. Justification of Specifications

The justification of the specification for each Quality Control tests conducted on the HPV vaccine final bulk and final container are provided below:

HPV vaccine Final Bulk

- **Sterility Tests:** The product needs to be sterile since it is a parental vaccine. The test specification is therefore set to “Absence of growth.”

HPV vaccine Final Container

- **Description:** The specification is set to best describe the physical appearance of the final product, i.e., a colorless supernatant and white deposit due the presence of aluminum salt sedimentation and a turbid liquid after shaking.

- **Identity HPV-16 L1 VLP and HPV-18 L1 VLP by -(b)(4)-:** This test is performed to confirm that the filling has been conducted with the appropriate material. The specifications are therefore set to “-(b)(4)-” for the HPV-16 L1 antigen and “-(b)(4)-” for the HPV-18 L1 antigen.

- **Sterility tests:** The product needs to be sterile since it is a parental vaccine. The test specification is therefore set to “Absence of growth”.

- **General safety tests- Abnormal toxicity on guinea pigs and on mice:**

Specifications have been set according ----- (b)(4) ----- /21 CFR610.12 and -(b)(4)- requirements.

----- (b)(4) -----

• **Volume:** The specification is set to ----- (b)(4) ----- per vaccine dose to ensure that the vaccine dose extracted from the syringe or the vial is injected with a volume of 0.5 ml.

----- (b)(4) -----

• **HPV-16 L1 VLP and HPV-18 L1 VLP *in vitro* relative potency by** (b)(4)-: The proposed specifications are ---- (b)(4) ---- for the HPV-16 L1 VLP and ---- (b)(4) ---- HPV-18 L1 VLP *in vitro* relative potencies. The specifications have been set based on calculations using (b)(4)- final container lots (clinical lots, development lots, non US and US commercial lots).

• **Aluminum content by** ----- (b)(4) -----: The proposed specification for aluminum content has been set at ---- (b)(4) ---- of the targeted value (--- (b)(4) --- per vaccine dose). This is in line with the specifications currently applied for other GSK Bio aluminum adsorbed vaccines.

----- (b)(4) -----

• **MPL content:** The proposed specification for MPL content has been set at ----- (b)(4) ---- of the targeted value (100 mcg/ml). This is in line with the specifications applied to other GSK Bio vaccines formulated with MPL. All lots produced during the development of the HPV vaccine and tested in clinical trials complied with this specification.

----- (b)(4) -----

(b)(4)

-(b)(4)-

(b)(4) _____

I found GSK's response to item 16 of our December 14, 2007 letter to be complete and adequate and I concur in general with the firm's rationale (and supportive data) for the basis for the proposed specification of -(b)(4)- for the test of "------(b)(4)-----
-----" performed on the *Cervarix* final container vaccine.

Impurities present in the Drug substances and the MPL -(b)(4)- are addressed in **Module 3.2.S.3.2 Impurities HPV-16 L1 VLP antigen** and **Module 3.2.S.3.2 Impurities HPV-18 L1 VLP antigen** and in **Module 3.2.A.3 Excipient**, respectively. See below Section IV for a discussion of the impurities present in MPL -(b)(4)-.

The Quality Control data for several batches of Process 4 commercial consistency final bulk and final containers (syringes and vials) are presented in several tables in the BLA in the Quality Module Section 3.2.r. Regional Information. In addition, batch data of representative Process 1, 2, 3 and 4 development vaccine lots are provided. The tests and the specifications listed in the batch data tables are those intended for the release of commercial HPV final bulks and final containers.

III.D.1.a.i.(b). Final Container

All HPV final bulks and final containers produced during development and for commercial consistency demonstration pass the specifications proposed for the release of commercial HPV final bulks and final containers.

III.D. STABILITY

III.D.1. STABILITY DATA, SUMMARY AND CONCLUSIONS

III.D.1.a. Long-term Stability Studies

III.D.1.a.i. Storage at +2 to +8°C

III.D.1.a.i.(a). Final Bulk

Stability data for Final Bulk (FB) lots -----(b)(4)----- are presented in Table 27. Data shows that the HPV commercial final bulk lots are stable for up to -(b)(4)----- when stored in -----(b)(4)----- tanks at ---(b)(4)---.

Table 27 Stability on HPV final bulk Process 4 commercial lot -(b)(4)----- after -----(b)(4)----- tank

TEST	Specifications	Lots	T0	T1
Sterility test FTM by b(4) b(4) (at 30-35°C)	Absence of growth	b(4)	Pass	Pass
			Pass	Pass
			Pass	Pass
Sterility test TSB by b(4) b(4) (at 20-25°C)	Absence of growth		Pass	Pass
			Pass	Pass
			Pass	Pass
Potency HPV-16 L1 VLP at b(4)	To be determined		1.23	0.92
			1.44	1.35
			1.13	1.40
Potency HPV-18 L1 VLP at b(4)	To be determined		0.79	0.99
			0.93	1.02
			0.97	1.63

1 US Consistency Commercial Lot described in LA

2 Manufactured at non-US manufacturing site via the Commercial Manufacturing Process

3 Manufactured at US Manufacturing Site via the Commercial Manufacturing Process

The testing of the FB after -(b)(4)- storage in -----(b)(4)----- tanks was performed on the FC immediately after filling. The time point -----(b)(4)----- for the FB corresponds to FC results at release (T0).

Based on the available stability data, the Company proposes a --(b)(4)-- shelf-life for the HPV final bulk upon storage at -----(b)(4)----- tanks.

The outlined information helps support the storage of the final bulk in -----(b)(4)----- tanks when stored at -----(b)(4)-----, followed by filling and storage of the final container (FC) at +2 to +8 °C for 36 months.

The final container lots have been followed in long-term, real-time stability studies at the recommended storage temperature of +2 to +8°C.

The currently available data on Process 4 commercial consistency lots (syringes and vials) show that they are stable for up to 24 months at +2 to +8°C.

The analytical procedures for the stability tests are those used for routine QC release or for characterization testing. They are described in **Module 3.2.P.5.1. Specifications**.

With respect to the AS04 adjuvant system, the lots are to be tested adequately and the specifications to be met are acceptable. They consist of the following:

Test	Specifications
Aluminum content by -----(b)(4)----- -----	-(b)(4)-----
-(b)(4)----- -----	-(b)(4)----- -----
MPL content by -----(b)(4)-----	-(b)(4)-----

With respect to post approval stability protocols, ----- (b)(4) ----- and per presentation is intended to be followed for real-time stability.

In addition, a stability protocol to support the storage of the first three HPV commercial final containers in glass syringes and in glass vials up to 36 months is planned.

The analytical methods used in the Stability Protocols are the Quality Control and characterization methods used for each of the materials tested.

Based on the overall stability results presented in **Section 2.3.P.8**, the Company proposes a shelf-life of 36 months for the HPV vaccines when stored at +2 to +8°C.

III.D.2. Conclusion Regarding Stability of HPV Final Container

The available stability data demonstrate that:

- Commercial scale final bulk lots are stable for up to -(b)(4)- when stored in --- (b)(4) ----- tanks at ----- (b)(4) -----,
- Available accelerated, cumulative and long-term real-time stability data show that the HPV vaccine is stable for up to 36 months when stored at +2°C to +8°C. These results support a shelf life of 36 months for the HPV vaccine, in syringes and vials, when stored at +2°C to +8°C.

For detailed conclusions regarding stability of the final product, see Dr. Robin Levis’s review.

III.E. Reference Standard(s)

An in-house MPL -(b)(4)- reference preparation is used as Reference Standard for the testing of MPL content by -(b)(4)-. This reference standard is a routine preparation of MPL ---(b)(4)--. The Reference Standards used in each of these tests are presented in Table 28.

Table 28 Reference materials used in QC testing of HPV final container

Tests	Reference material
b(4)	Reference: commercial purified bulk batch b(4)
	Reference: commercial purified bulk batch b(4)
<i>In vitro</i> relative potency by b(4)	Reference: commercial final container lot b(4)
MPL content by b(4)	Reference: commercial MPL b(4) bulk b(4)

In the Resubmission (Serial 48), the firm reports that many of the reference standards instrumental in testing of key aspects of the drug product will run out during 1Q/2Q2009. To avoid any impact this may have on the production of launch supplies, GSK validated new standards for use in the manufacturing process. Each standard was tested, as per the available validation protocols, and results compared to current validity criteria. This included the replacement of the current MPL liquid bulk reference standard.

III.E.1 Validation of a -----(b)(4)----- Reference Material

-(b)(4)-----

-(b)(4)-----

Batch analysis data are provided in Table 29.

-(b)(4)-----

[
--(b)(4)--
]

FDA Reviewer's comment:

All of the results for batch -----(b)(4)----- complied with the acceptance criteria. The validation protocols that describe the methods used to validate the new reference standards along with test results were included in m3.2.P.6 Reference Standards or Materials (HPV Vaccine, GSK Biologicals) and Annexes 7 and 8 of m3.2.R Regional Information. These data were reviewed and found to be acceptable.

IV. MPL -----(b)(4)-----

----- (b)(4) -----

----- (b)(4) -----

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----- (b)(4) -----

Page 40 – Review of MPL-Relevant CMC Information in Cervarix BLA (STN 125259)

Ten (10) pages determined to be non-releasable: (b)(4)

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----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

All product containers are 100% inspected manually by (b)(4)- inspectors for defects prior to being labeled in *MPL* Labeling. After inspection, all product containers are hand-labeled using QC inspected and controlled labels.

IV.D.1.b. Labeling, Storage, Packaging and Finished Goods Warehousing

The product is labeled in MPL Labeling and stored in a Controlled -(b)(4)- Temperature -(b)(4)- refrigerator in the Warehouse area. Packaging of product for shipment is done in Packaging, at which time the product is transferred for distribution via Shipping and Receiving.

IV.D.2. Description of Manufacturing Process and Process Controls

(b)(4)

Page 43 – Review of MPL-Relevant CMC Information in Cervarix BLA (STN 125259)

31 pages determined to be non-releasable: (b)(4)

V. REFERENCES

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