

DEPARTMENT OF HEALTH & HUMAN SERVICES



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: File BL STN 125259/0

From: Rebecca Olin, OCBQ/DMPQ/MRB2

Through: Chiang Syin, PhD, Chief, CBER/OCBQ/DMPQ/MRB2

Subject: GlaxoSmithKline Biologicals (License # 1617) BLA: Cervical cancer vaccine for the active immunization of females 10-25 years of age.

Action Due: September 29, 2009

Action Recommended

Based upon my review of this and all related submissions, I recommend approval of BLA STN 125259/0.

Product

Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant (proposed trade name Cervarix™)

Summary

GSK submitted this BLA in support of the manufacture of HPV Vaccine at the manufacturing facilities in Wavre Nord and Rixensart, Belgium. Cervarix contains recombinant C-terminally truncated L1 proteins of human Papillomavirus Type 16 and Type 18 each assembled separately as virus-like particles (VLP) and produced on -(b)(4)- cells.

Monovalent bulks are manufactured in Wavre Nord at a new dedicated facility (-(b)(4)-) built for HPV manufacturing purposes. Monophosphoryl Lipid A (MPL) bulk is received from the GSK facility in Hamilton, MT and is further manufactured at the Rixensart. Formulation occurs at licensed buildings -(b)(4)- and -(b)(4)- located in Rixensart. Filling occurs in approved facilities at -(b)(4)- and -(b)(4)-. Labeling and packaging are conducted in Wavre Nord (-(b)(4)-).

This BLA is submitted for the approval of Cervarix for the immunization of girls, adolescent and adult females from 10 years of age onward for the prevention of squamous-cell carcinoma and adenocarcinoma of the cervix caused by oncogenic human papillomaviruses (HPV) types 16 and 18. The vaccine is a preservative-free product available as a 0.5 mL single-dose in 3 mL glass vials and as a 0.5 mL single-dose in pre-filled TIP-LOK® disposable 1.25 mL glass syringes.

The Pre-License inspection, dated September 12-21, 2007, resulted in the issuance of an FDA-483. The firm responded and answers were acceptable.

I reviewed the facilities and equipment sections of the original submission in additions to the following amendments:

Amendment 5:	Removal of the -(b)(4)- vial filling line from the BLA
Amendment 67:	Response to the FDA-483
Amendment 42:	Intent to submit Class 2 Resubmission including a Comparability Protocol for a -----(b)(4)-----.
Amendment 47:	Comparability Protocol for -----(b)(4)-----
Amendment 57:	Response to Hamilton, MT FDA-483
Amendment 67:	Withdrawal of CP for -----(b)(4)-----

Review of the Comparability Protocol for the -----(b)(4)----- revealed an identical CP was submitted for the firm's currently licensed products. GSK received a CR letter for this CP which was not reported and the corrective actions completed as a result of the CR were not submitted to the BLA. GSK has withdrawn the CP from this BLA and will submit it as a stand alone CP at a later date.

Information requests relayed to the firm were addressed satisfactorily. Review of the data in this file and the results of the pre-approval inspection show that the facility is in a state of control. Based on these findings, I recommend this file be approved.

Information Requests

1. Regarding the Container Closure systems for Cervarix – you state that the Container Closure systems proposed for Cervarix are identical to those used on other commercial vaccines manufactured by GSK.
 - Please identify these commercial products and indicate what products using the vial, syringe and stoppers used for Cervarix are licensed in the US.
 - Please provide the descriptions for the container closure systems specific to Cervarix. Section 3.2.P.7 appears to cover several types of syringes, stoppers and vials.
 - Provide an overview of the testing and test results conducted specifically to the Container Closure systems to be used with Cervarix. The tests included in Section 3.2.P.7 appear to cover several types of syringes, stoppers and vials. Please include:
 - Extractables and Leachables
 - Sterilization
 - Container closure integrity testing
 - Lubrication

- ## Review Narrative

Facilities that are currently licensed and used for the production of HPV Vaccine include -----(b)(4)----- located at the Rixensart site and -----(b)(4)----- located in Wavre.

Licensed filling operations in -----(b)(4)----- include all of the products listed above as well as Fluarix which is filled on syringe lines -----(b)(4)-----.

The focus of this Review Memo will be on the new Wavre bulk manufacturing facility – (b)(4)-.

Manufacturing Process

Manufacturing is conducted in -(b)(4)- phases:

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

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

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

A series of vaccine manufacturing developments were made prior to the selection of the final process for commercial operations. Process optimizations lead to four antigen production processes and to four corresponding vaccine manufacturing processes referred to as Process 1 to Process 4. The process that will be used to produce commercial lots after licensing will be Process 4.

Drug Substance

HPV 16 & 18: The HPV-16/18 L1 VLP antigen is prepared using a novel technology in which the L1 proteins are produced upon infection of the ----(b)(4)---- *Trichoplusia ni* insect cell line with the recombinant HPV-16/18 L1-encoding Baculovirus.

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

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

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

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

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

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

Drug Product

The final product contains the following:

Ingredients	Quantity (per 0.5 ml dose	Function
Active Ingredients		
HPV-16 L1 VLP	20 µg	Antigen
HPV-18 L1 VLP	20 µg	Antigen
Excipients		
MPL	50 µg	Immunostimulant
Aluminum Hydroxide	500 µg	Adjuvant
Sodium Chloride	4.4 mg	Buffer
Sodium dihydrogen phosphate dihydrate	0.624 mg	Buffer
Water for Injection	qs	Solvent

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.

Manufacturers

The following manufacturers are involved in the manufacture of Cervarix:

Site	Responsibility
GSK Biologicals SA (Belgium) Parc de la Noire Epine Rue Fleming 20 1300 Wavre	------(b)(4)----- ----- ----- ----- ----- ----- -----
GSK Biologicals SA (Belgium) Rue de l’Institut 89 1330 Rixensart	------(b)(4)----- ----- -----
GSK Biologicals North America Hamilton, MT	------(b)(4)----- -----

Bioburden

Bioburden samples are taken -----(b)(4)----- of the HPV VLP purified bulks and -----(b)(4)----- of the -----(b)(4)----- . Bioburden results were reviewed during the PAI and no deficiencies were noted.

Endotoxin

Endotoxin content by -----(b)(4)----- method is conducted prior to the release of -----(b)(4)----- . The release criteria is ----(b)(4)--- of protein. This corresponds to a limit of -----(b)(4)----- protein of HPV-16 L1 VLP antigen in one vaccine dose. Endotoxin results for ----(b)(4)----Phase III development batches for HPV 16 and HPV18, respectively and 5 consistency batches for both types showed all results were within acceptance criteria.

Endotoxin testing is not conducted on the final product as a release test. The drug product contains HPV-16 L1 VLP and HPV-18 L1 VLP antigens adjuvanted with AS04 composed of Aluminum and monophospholipid A (MPL). MPL is a purified, non-toxic endotoxin derivative prepared from the lipopolysaccharide of Salmonella minnesota R595 strain. Due to the presence of the MPL endotoxin-derivative in the drug product, a proper evaluation of potential endotoxin activity in the final bulk and/or the final container is hampered and was thus not included in the tests performed in the release specification of the drug product.

Sterility Testing

Sterility testing is conducted at the following process steps:

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

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

- HPV Final Bulk Vaccine
- HPV Final Container

For each of the above steps, sterility testing was conducted with FTM by ----- (b)(4) ----- at 30-35 °C and with TSB by ----- (b)(4) ----- at 20-25 °C in accordance with -(b)(4)- requirements.

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

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

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

HPV Final Bulk Vaccine: Batch analysis results for HPV commercial consistency final bulk lots show that the three lots manufactured showed passing results for sterility.

HPV Final Container: Batch analysis results for HPV commercial consistency final container lots for syringes and vials show that the three lots manufactured for each container system showed passing results for sterility.

Process Validation

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

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

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

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

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

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

Media fill data was included in the submission for filling lines ----- (b)(4) ----- . A minimum of - (b)(4) - units per simulation were filled and incubated at ----- (b)(4) ----- . Data presented show no growth was found in any container. Media fills were reviewed during the PAI and no deficiencies were noted.

Container Closure System

The finished vaccine is filled into a 1.25 ml glass syringe, stoppered with grey ----- (b)(4) ----- stoppers or in 3 ml glass vials, stoppered with grey ----- (b)(4) ----- stoppers and capped with aluminum flip-off caps. These container closure configurations are also used for Engerix-B, Havrix, Twinrix, Infanrix, Pediarix, Boostrix, Kinrix, and Fluarix.

Syringes and stoppers: The Cervarix syringe is composed of a Type - (b)(4) - glass 1.25 mL syringe barrel (----- (b)(4) -----) adapted with a ----- (b)(4) ----- closure system and --- (b)(4) --- tip cap, stoppered with a --- (b)(4) --- plunger stopper (--- (b)(4) ---). The type - (b)(4) - glass used in the manufacture of the syringe barrel is in compliance with the current - (b)(4) - (Containers - Glass), and the ----- (b)(4) --- grey ----- (b)(4) --- has been qualified according to the biological tests of the current ----- (b)(4) -----.

The 1.25mL syringe ----- (b)(4) --- is sterilized by ----- (b)(4) ----- sterilization. The ----- (b)(4) --- validation has been performed according to --- (b)(4) --- to achieve a ----- (b)(4) ----- residue is less than - (b)(4) - according to the ----- (b)(4) -----

The plunger stopper sterilization is performed by ----- (b)(4) ----- according to - (b)(4) - and ----- (b)(4) -----.

the lubricant used for the plunger stopper is ----- (b)(4) -----, which meets the current requirements of USP-NF Monograph. The maximum specification

Additionally, extractable studies have been performed on the syringe plunger stopper and vial stopper by the supplier and GSK Bio, respectively, and all results met the requirements as

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

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

Primary Manufacturing Facility

Production of the bulk antigen takes place at Wavre-Nord in Building -(b)(4)-. The production of HPV-16 L1 VLP and HPV-18 L1 VLP antigen purified bulks are divided into -(b)(4)- main streams:

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

Secondary Manufacturing Facilities

The manufacture for formulation and filling of the vaccine is divided into -(b)(4)- parts:

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

Secondary manufacturing are conducted in Buildings ----- (b)(4) -----.
These manufacturing facilities are currently licensed.

Building -(b)(4)-

Building -(b)(4)- is a new facility specifically designed to manufacture bulk which is used for the bulk production of Human Papillomavirus (HPV). This building ----- (b)(4) -----

Product contact equipment used in -(b)(4)- includes:

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

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

(b)(4)

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(b)(4)

(b)(4)

The WFI systems for Buildings -----(b)(4)----- are currently licensed for GSK's existing US products.

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

Validation of the PW system involved (b)(4)- cycles of testing conducted over --- (b)(4) ---
----- . Samples were tested for microbials, endotoxin, TOC, conductivity, nitrates and

heavy metals. Critical points such as -----(b)(4)----- were tested -(b)(4)- for
microbials, endotoxin, TOC and conductivity. Test results showed two failures for total germ
count above the acceptance criteria of -----(b)(4)----- . Corrections were made and -(b)(4)-
additional sampling days were added to each failed use point with passing results.

An additional validation study was conducted to include new use points supplying the
autoclave technical areas in the laboratory, purification, wrapping, culture and washing rooms.
Results for the -(b)(4)- days of testing were passing for microbials, endotoxin, TOC,
conductivity, nitrates and heavy metals.

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

-- -----

Conductivity is measured at the -----(b)(4)----- .
There are -(b)(4)- use points.

Validation included -(b)(4)- cycles or phases of -----(b)(4)----- in which samples are
tested for microbials, endotoxin, TOC, conductivity, nitrates and heavy metals. Phase 1
includes -(b)(4)- days of testing when the system was not in use. Phase 2 testing was
conducted for -(b)(4)- day either under routine conditions or under simulated routine use of the
WFI system. Phase 3 testing includes an additional -(b)(4)- days of testing under simulated or
routine WFI production. Three types of sampling were conducted: -----(b)(4)-----.

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

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

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

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

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

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

Data summaries were provided including test results for each day of each phase. All results were passing with no deviations noted.

Additional validation studies were conducted to include new use points. Test results were within acceptance criteria for these studies. A validation study referred to as the fourth phase validation included a (b)(4)- day sampling schedule in which each point was sampled (b)(4)- times in the (b)(4)- days and tested for the full battery of tests. This validation was conducted when the facility HVAC systems were operational and verified water quality at all use points under routine operating conditions. Data summaries show one excursion occurred which required repair of the sample piping. An additional (b)(4)- days of testing at that use point showed passing results for all testing.

HVAC

The production rooms on level (b)(4)- in Building (b)(4)- are each supplied with air through dedicated air handling units. Rooms exposed to live virus are supplied with (b)(4)- fresh air and exhaust air is vented through ULPA filters (99.99%).

Rooms exposed to live virus in Building (b)(4)- include:

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

Classifications of rooms in the production area include:

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

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

Five (5) pages determined to be non-releasable: (b)(4)