**Summary Basis for Regulatory Action**

**From:** Helen S. Gemignani, Chair of the Review Committee

**BLA/ STN:** 125259/132

**Applicant Name:** GlaxoSmithKline Biologicals, Inc.

**Date of Submission:** September 21, 2010

**PDUFA Goal Date:** July 22, 2011

**Proprietary Name/ Established Name:**
Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant/CERVARIX®

**Additional Indication Sought Under This BLA Supplement:** The applicant sought to extend the current indication, from females 10 through 25 years of age, to include 9 year old females.

**Recommended Action:** Approval is recommended for extension of the current indication for CERVARIX to include use in females 9 through 25 years of age.

**Signatory Authorities Action:** Approval of recommended action

**Offices Signatory Authority:**

Wellington Sun, M.D.
Director, Division of Vaccines and Related Products Applications
Office of Vaccine Research and Review

**√ I concur with the summary review.**
**□ I concur with the summary review and include a separate review to add further analysis.**
**□ I do not concur with the summary review and include a separate review.**

**Table 1: Review documents used in compiling this SBRA:**

| Review Category | Reviewer |
|---|---|
| Clinical Review | Nancy B. Miller, M.D. |
| Statistical Review | Martha Lee, Ph.D. |
| Labeling Review | Dana Jones |
| Bioresearch Monitoring Review | Dennis Cato |
| Epidemiology | Michael Nguyen, M.D. |

## 1. Introduction

CERVARIX® is a non-infectious recombinant bivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of human papillomavirus (HPV) Types 16 and 18 with a proprietary adjuvant system. CERVARIX was licensed in the United States on October 16, 2009 and is currently indicated for females 10 through 25 years of age for the prevention of:

- cervical cancer,
- cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ*, and
- cervical intraepithelial neoplasia (CIN) grade 1.

In September of 2010, GlaxoSmithKline Biologicals, Inc. (GSK) submitted this Biologics License Application (BLA) supplement STN 125259/132, to expand the indication of CERVARIX to include females 9 years of age and to revise accordingly the Indications and Usage sections of the Package Insert.

## 2. Background

In the United States, recommendations from the Advisory Committee on Immunization Practices (ACIP), of the Centers for Disease Control, indicate that females as young as 9 years of age may receive HPV vaccination at the discretion of their physician. With this BLA supplement, GSK is seeking approval to include females as young as 9 years of age in the indicated age population.

The CERVARIX BLA approval letter dated October 16, 2009, advised GSK of the pediatric study requirement to perform a postmarketing study in females 9 years of age, pursuant to Section 505B(a) of the Food Drug and Cosmetic Act and noted GSK's commitment to submit the final clinical study report for the aforementioned study by June 30, 2010.

In order to meet the June 30 deadline, the required clinical study report for study HPV-048 was submitted to the BLA on June 17, 2010, as "General Correspondence." In addition, a supplemental study report for study HPV-048, entitled: "*Supplemental Report to Clinical Study Report for Study 110659 (HPV-048): Evaluation of the safety and immunogenicity of GlaxoSmithKline Biologicals' HPV vaccine 580299 when administered in healthy females aged 9 - 25 years using an alternative schedule and an alternative dosing as compared to the standard schedule and dosing*" was also submitted

at that time. A letter was issued by CBER on June 15, 2011, acknowledging that GSK had fulfilled the pediatric study requirement by submitting a final clinical study report for the postmarketing study conducted in females as young as 9 years of age.

In September of 2010, GSK submitted this BLA to expand the indication of CERVARIX to include females 9 years of age and to revise accordingly the Indications and Usage sections of the Package Insert. The study reports and associated datasets from study HPV-048 (including the HPV-048 Month 7 Clinical Study Report, dated March 20, 2009, and the HPV-048 supplemental study report, which presents *post-hoc* immunogenicity analyses requested by CBER) were the subjects of this review and served as the basis for the recommendation of approval.

## 3. Chemistry Manufacturing and Controls (CMC)

A full CMC review of the product was completed at the time that CERVARIX was originally licensed in October 2009. No new CMC data were requested or submitted in the context of this submission.

## 4. Nonclinical Pharmacology/Toxicology

A full nonclinical pharmacology/toxicology review of the product was completed at the time that CERVARIX was originally licensed in October 2009. No new pharmacology or toxicology data were requested or submitted in the context of this submission.

## 5. Clinical

Clinical data from a single study (HPV-048) was submitted to this supplement in support of the proposed expansion of the indication. In addition to data from Study HPV-019, the clinical reviewer re-analyzed relevant data from studies in young adult women, including from Studies HPV-013 and HPV-015.

*Efficacy/Immunogenicity*

The immune responses to HPV-16 and HPV-18 elicited in 9-14 year old females are non-inferior to the immune responses elicited in 15-25 year old females (similar to comparisons between 10-14 year old females and 15-25 year old females in the original Cervarix Biological Licensing Application). Therefore, efficacy is inferred in subjects 9-14 years of age based on these analyses.

*Safety*

Based on the review of study HPV-048, the safety profile of Cervarix in females 9-25 years of age is generally comparable to the safety profile of Cervarix in females 10-25 years of age, the dataset that supported initial licensure of the product in 2009. Furthermore, there were no noteworthy differences in safety in pediatric subjects 9-17 years of age compared to adult females 18-25 years of age. Additional post-marketing safety data requested in the pediatric age group was also supportive of extending the lower age indication to include females as young as 9 years of age.

*Clinical Reviewer Overall Conclusions*

The clinical reviewer recommends approval of this supplement and revisions to the package insert to include clinical data regarding use in females as young as 9 years of age.

**6. Statistical**

The statistical reviewer evaluated a *post-hoc* analysis to assess non-inferiority of the immune response after the third dose of CERVARIX (administered at Months 0, 1, 6) in 9-14 year old subjects vs. 15-25 year old subjects. Non-inferiority of the immune response was to be demonstrated if the lower limit of the 95% confidence interval (CI) of the GMT ratio of the 9-14 year old subjects over the 15-25 year old subjects was above the pre-defined limit of 0.5.

The statistical reviewer concluded that non-inferiority of *Cervarix* in 9-14 year old subjects vs. 15-25 year old subjects with respect to anti-HPV-16 and anti-HPV-18 GMTs was demonstrated, since the lower limit of the 95% CI of the GMT ratio for subjects 9-14 years vs. 15-25 years was above the pre-defined limit of 0.5.

**7. Bioresearch Monitoring**

Review of the data submitted with this BLA supplement did not require Bioresearch-monitoring (BIMO) Clinical Investigator Inspection Assignments. The data show a small number of evaluable 9 year old subjects enrolled at 8 sites in Germany and Canada. BIMO inspections were not conducted for this BLA supplement but were conducted for the original BLA for this product.

**8. Labeling**

Appropriate changes were made to the Indications and Usage sections of the Package Insert to describe the data that support lowering the age indication to include use in females 9 through 25 years of age. The upper age limit has not changed (25 years of age). In the package insert, safety data from the pediatric subjects 9-14 years of age (n=82) were incorporated into the totals within the safety tables for solicited and unsolicited adverse events. Overall percentages of adverse events reported in subjects 10-14 years of age did not change to any appreciable degree after incorporation of data from these subjects. Similarly, safety data from subjects 15-25 years of age (n=157) from Group 1 were incorporated into totals for subjects 15-25 years of age. In addition, non-inferiority of immune responses in 9-14 year old and 15-25 year old subjects was added to section 14.4 in the package insert.

**9. Postmarketing**

GSK submitted an updated pharmacovigilance plan (PVP) with this BLA supplement. The revised PVP includes an updated safety specification, cumulative analyses of passive

surveillance data, and interim results of the CERVARIX Pregnancy Registry. A comprehensive review of these post-licensure activities did not identify new safety concerns.

The updated PVP also included the two new studies requested by FDA at the time of initial US licensure in October 2009. These studies were designed to address two theoretical safety risks in the indicated population: autoimmune diseases and spontaneous abortions. The review committee believes that the current PVP remains adequate for ongoing safety monitoring of CERVARIX post-licensure. FDA has requested only that a minor change be made to improve postmarketing surveillance of the proposed expanded age group in this BLA. Accordingly, GSK has agreed to include females 9 years of age in the existing study for autoimmune diseases. Thus, a postmarketing commitment (PMC) will be implemented to include 9 year old females in the applicant's ongoing PMC study to follow any theoretical safety risks related to autoimmune disease, HPV-EPI-015. Two additional PMCs will be implemented for submission of final clinical study reports for co-administration studies, HPV-029 and HPV-030.

The UK experience with CERVARIX provides the most substantial and robust safety to date. The MHRA has reviewed these data and conclude that the vaccine's safety profile is consistent with the clinical trial data and presents no new safety issues.

No new safety issues were identified in the analysis of the clinical data for 9- 25 year old females.

A number of other postmarketing commitments, from the original BLA approved in October 2009, are in the process of being fulfilled. FDA maintains on its website a tool for tracking progress on postmarketing commitments and requirements: http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

**10. Recommendation**

The review committee recommends approval of the supplement to extend the current indication for CERVARIX to include use in females 9 through 25 years of age.