Summary Basis of Regulatory Action

Date: October 15, 2009

From: Robin Levis, Ph.D., Chair of the Review Committee

BLA/ STN#: 125259/0

Applicant Name: GlaxoSmithKline Biologicals (GSK)

Date of Submission: March 29, 2007

Complete Response Letter Issued: December 14, 2007

Date of Re-submission: March 30, 2009

PDUFA Goal Date: September 29, 2009

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

Indication: CERVARIX is indicated for use in females 10 through 25 years of age, for the prevention of the following diseases caused by Human Papillomavirus (HPV) types 16 and 18:

- Cervical cancer
- Cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Norman Baylor, Ph.D., Director, 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.**

Material Reviewed/ Consulted **Specific documentation used in developing the SBRA**	**Reviewer Name – Document(s) Date**
Clinical Review	Nancy Miller, MD – 10/2009
Statistical Review	Martha Lee, Ph.D. – 8/07, 9/08, 10/08, 7/09 Lev Sirota, Ph.D. – 7/09
CMC Review	Robin Levis, Ph.D. – 9/09

	Elizabeth Sutkowski, Ph.D. – 10/09
Pharmacology/ Toxicology Review	Steven Kunder, Ph.D. – 5/08 Elizabeth Sutkowski, Ph.D. – 9/09 Marion Gruber, Ph.D. – 8/09
Advertising and Promotional Labeling	Helen Gemignani – 9/09 Lisa Stockbridge, Ph.D. – 7/09, 9/09
Biomonitoring Biorearch Monitoring Review	Solomon Yiman, Ph.D. – 9/08
Establishment Inspection Report	Gang Wang, Ph.D. – 9/09 Rebecca Olin, RN – 9/09 Robin Levis, Ph.D. – 10/09
Postmarketing Surveillance	Michael Nguyen, MD – 9/09

1. Introduction

GlaxoSmithKline Biologicals submitted biologics license application (BLA) 125259 on March 29, 2007. This BLA is a request for licensure of a bivalent vaccine, CERVARIX, to prevent cervical cancer caused by human papillomavirus (HPV) types 16 and 18. This BLA included data on product development and characterization, manufacturing process validation and details of all in process and quality control testing to ensure the safety, purity, potency of product intended for release to market. In addition, this BLA included pre-clinical and clinical data to support the efficacy and safety of the product. A complete response letter was sent to the sponsor on December 14, 2007. Additional information requested in this letter was related to all aspects of the review, but the critical requests were related to assessments of product safety. The sponsor submitted a full response to the complete response letter on March 30, 2009.

This document includes summaries of each of the major review disciplines associated with the review of this BLA and highlights the major issues covered and brought to resolution during the review process for CERVARIX. These include:

- The safety profile of the novel adjuvant, AS04, and the potential for adverse events related to neuroinflammatory and autoimmune events.
- The imbalance noted in spontaneous abortions in trial participants who became pregnant near the time of immunization.
- Determination of the indications to be listed in the label, including an indication for the prevention of disease caused by non-vaccine HPV types.

2. Background

CERVARIX is composed of recombinant C-terminally truncated HPV-16 L1 and HPV-18 L1 proteins, assembled into virus-like particles (VLPs) and adjuvanted with GlaxoSmithKline Biologicals' proprietary adjuvant system, AS04. 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 AS04 adjuvant is composed of an aluminum salt, $Al(OH)_3$ and 3-*O*-desacyl-4'-monophosphoryl lipid A, (MPL). The MPL immunostimulant is a detoxified derivative of the lipopolysaccharide of the gram negative bacterium *Salmonella minnesota* R595 strain.

One dose of CERVARIX contains 20 ug of HPV-16 and 20 ug of HPV-18 proteins adjuvanted with AS04, composed of 500 ug aluminum hydroxide and 50 ug MPL. The vaccine does not contain preservative and is available as a 0.5 mL single-dose in 3 mL glass vials (fill volume = -b(4)-ml) and as a 0.5 mL single-dose in pre-filled, TIP-LOK® disposable 1.25 mL glass syringes (fill volume = -b(4)- ml). The proposed shelf life is 36 months and the date of manufacturing starts from the filling date of the final container.

This vaccine is intended for use in females 10 through 25 years of age with an administration schedule of a single dose at 0, 1 and 6 months.

3. Chemistry Manufacturing and Controls (CMC)

Place of Manufacture: The vaccine is manufactured at two locations:
GlaxoSmithKline Biologicals SA
Rue de l'Institut 89
1330 Rixensart
Belgium

GlaxoSmithKline Biologicals SA
Parc de la Noire Epine
Rue Fleming, 20
1300 Wavre
Belgium

The initial procedure for HPV L1 antigen production was developed at MedImmune, Inc. IND-(b)(4)-, submitted September 9, 1998, was originally sponsored by MedImmune. Antigen bulks manufactured at MedImmune, Inc were used for phase 1 and 2a studies. In 2000, the technology was transferred to GSK Biologicals, where phase 2b and phase 3 clinical materials were prepared. The final antigen production process was developed and validated at GSK.

The manufacturing process for the production of the HPV L1 proteins is based on the inoculation of an insect cell substrate, -----(b)(4)----- cells, derived from *Trichoplusia ni* cells, with recombinant baculoviruses expressing either HPV 16 or HPV 18 L1 proteins. The L1 protein is purified from the inoculated cells via a series of filtration and chromatography steps that have been optimized to remove cell substrate and baculovirus contaminants, while yielding a highly purified preparation of the L1 antigen. The L1 antigen is then assembled into virus like particles (VLPs). These L1 particles have been well characterized and have been shown to have structural and immunological properties identical to wild type virus. Once assembled, the VLPs are adsorbed to aluminum hydroxide, making the adsorbed monovalent bulk drug substance. Stability data is included in the submission to support the storage of these bulks for ---------(b)(4)---------- under the appropriate conditions.

Final drug product formulation entails preparing the AS04 adjuvant and combining the adjuvant with each of the HPV VLP adsorbed bulks ----------(b)(4)----------
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----------. The MPL is then adsorbed to aluminum hydroxide. Stability data is included in the submission to support the storage of the final formulated bulk for ---(b)(4)--- under the appropriate conditions. The product is ultimately filled into either single use vials or single use syringes. Stability data is included in the submission to support the requested shelf life for final product for 36 months at 2° to 8º C.

a) Product Quality – Critical elements of the product information, included in the BLA, are related to the novel aspects of the product, the characterization of the cell substrate, the adjuvant, and the L1 VLPs, validation of the manufacturing process for the L1 proteins and the MPL, development of appropriate quality control testing plan to ensure manufacturing consistency and final container product quality, and stability data to support the hold times for intermediates and bulks, and to support the requested shelf life for the product once released for market distribution. Data and information included in the BLA demonstrate that the manufacturing process is well controlled. Detailed below are some of the critical aspects of the product review.

Characterization of the -(b)(4)- cell line: ---------------------(b)(4)-----------------------
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The manufacturing process for this vaccine is novel in two ways. The first is the use of the baculovirus expression system to produce the respective L1 proteins. As this is the first product under review for licensure using an insect derived cell line, in addition to the QC testing to verify the identity, purity and safety of the -----(b)(4)----- cell lines, extensive studies were performed to characterize the biological properties of the cell lines. Results from these studies demonstrate that this cell substrate is appropriate for use in the production of HPV L1 proteins and that there are no safety concerns related to adventitious agents or product contamination based on the cell substrate.

The second novel aspect of this product is the use of the AS04 adjuvant. This product will be the first licensed in the Unites States using this adjuvant system. The sponsor included detailed manufacturing data and characterization of the MPL, which is a component of this adjuvant. Information on the safety profile of the MPL was included as the MPL precursor molecule, lipopolysaccharide A has shown inflammatory properties that could potentially affect the safety of the final vaccine product. In addition, multiple preclinical studies were performed in animals to determine the advantage of including the adjuvant and to determine the safety and mode of action of the adjuvant.

Product Stability and Shelf Life - Stability data for the storage of each intermediate and final container are supportive of the stability of the product at each stage of the manufacturing process. This includes data for -------------------(b)(4)----------------------
---, and final container drug product storage for 36 months at 2° – 8°C. In discussion with the

sponsor, CBER required a cumulative stability study to support the shelf life of the product over the entire storage profile of the product. The requirement for this study was established to verify ----------(b)(4)----------, in addition to the final container storage at 2° – 8°C. This study would include data on ----------(b)(4)----------, and 36 months of final product. This study is currently underway and final data will be submitted to the BLA as a post-marketing commitment (see below). The stability of the ----------(b)(4)----------. The cumulative stability study will also include the use of ------(b)(4)--------. The sponsor would like to establish a ----------(b)(4)----------. This study is ongoing and results will be submitted as a PMC as detailed below.

Clinical Assays – The CMC review of this file also included a review of all relevant clinical assays used to measure the HPV infection and immune status of trial participants at the time of entry into the clinical studies and post immunization. A type specific, multiplex PCR/LiPA has been developed by the sponsor to detect HPV DNA in samples from trial participants. An ELISA assay has been developed to detect anti-HPV 16 and 18 antibodies in serum samples from trial participants. All assays used for the evaluation of clinical trial specimens were adequately validated and are performed using appropriate controls.

b) CBER Lot Release – Two lot release protocols were submitted to the BLA for review. These initial protocols submitted for review included one protocol that detailed in-process and final release tests performed for adsorbed monovalent bulks of HPV type 16 and type 18 VLPs and for the final MPL bulk drug substance batches, and one protocol that detailed the quality control release testing on the final container drug product vials or syringes. It was determined through discussion with the sponsor that each of the adsorbed monovalent bulks would be used for a single final container lot and therefore we advised the sponsor to combine all information related to a single final container lot into a single lot release protocol. In addition to the requested changes in the format of the lot release protocol, we requested that the sponsor include some additional quality data on the --------(b)(4)---------- lots used to -----(b)(4)----------, and that the sponsor include a test for mycoplasma that includes the test for -------(b)(4)---------. The sponsor accepted all requested changes to the protocol and submitted the final protocol for review on September 1, 2009. CBER will release final container lots of CERVARIX.

Internal discussions were held at CBER to determine the testing plan for lots submitted for release to market. The lot release testing plan was finalized in a meeting between CBER/OVRR Division of Viral Products and CBER/OVRR Division of Product Quality, held June 16, 2009.

The final testing plan details the quality testing conducted by the sponsor and makes recommendations of testing to be conducted at CBER. The CERVARIX testing plan

includes testing to be conducted at CBER on the first three lots after licensure. These tests are:

1. Test for Aluminum Content by atomic absorption spectroscipy
2. Test for MPL Content by Gas Chromatography
3. Potency Test by ELISA

Additional testing deemed necessary will be conducted by CBER,. This includes testing up to 10% of all lots submitted during the first year of licensure and then re-evaluating the needed testing frequency. All testing will be performed by OVRR/DPQ.

c) Facilities review/inspection – Two inspections were held to support the review and licensure of this product. The first inspection was held at GSK Biologicals in Belgium. The inspection was conducted from 09/12 – 21/2007. The facility information for this site is:

GlaxoSmithKline Biologicals S.A.
Parc de la Noire Epine
Rue Fleming 20
1300 – Wavre, Belgium
FEI # 3002875226

This facility is where the L1 VLPs are manufactured and ---------(b)(4)----------
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---. In process and final container quality testing for the HPV antigens and MPL is performed here. Overall, this facility was considered to be within compliance and all processes were well controlled. This inspection concluded with the presentation of a 483 containing three items. These items were related to the adherence to the change control SOP, cleaning validation of formulation tanks, and data errors identified in the BLA. All items in the 483 were appropriately addressed by the sponsor (detailed in an amendment to the BLA, submitted October 17, 2007) and the compliance status of this site is deemed acceptable for product approval.

The second inspection was held at GSK Biologicals, North America in Hamilton, Montana. The inspection was conducted from 06/23 – 26/09. The facility information for this site is:

GlaxoSmithKline Biologicals, North America
533 Old Corvallis Road
Hamilton, MT 59480
FEI # 3024448

This facility is the location where MPL is manufactured. An inspection was conducted at this location to evaluate the manufacturing process for MPL. Overall, the facility was in compliance and the MPL manufacturing process and testing were well controlled. This inspection concluded with the presentation of a 483 containing four items. These items were related to dirty equipment hold times, incomplete deviation investigation, failed cleaning validation, and insufficient records to verify employee training. The firm submitted responses to the 483 (detailed in an amendment to the

BLA, submitted July 24, 2009). All responses were detailed and included target dates for completion. All items were appropriately addressed and the compliance status of this site is deemed acceptable for product approval.

d) Environmental Assessment A request for a categorical exclusion from an Environmental Assessment under 21 CFR § 25.31(c) was submitted to the BLA. It was concluded that the request was justified as the product is composed of naturally occurring substances and that no extraordinary circumstances exist, which would require an environmental assessment.

4. Preclinical Pharmacology/Toxicology

Extensive preclinical pharmacological, pharmokinetic, and toxicology testing was performed on the components of this vaccine, independently and as formulated in the final drug product. These studies were important for demonstrating the immune potential of the vaccine and the initial safety of the vaccine plus and minus the adjuvant. One critical component of this vaccine is the novel adjuvant, AS04. This adjuvant has not previously been used in a product licensed in the United States. Due to the use of this novel adjuvant, a series of preclinical studies were also performed on MPL and the AS04 components individually.

Four separate reviewers were involved in evaluating the preclinical studies performed on this product. These reviewers provided reviews on:

- Immunogenicity and pharmacodynamics of the vaccine formulation and of the AS04 adjuvant.
- Safety and repeat dose toxicity studies performed using the final vaccine formulation.
- Safety and repeat dose toxicity studies performed using the MPL adjuvant.
- Reproductive toxicity studies using the final vaccine formulation as well as MPL only.

Summary of immunogenicity and pharmacodynamics studies on the vaccine and adjuvants: These studies included an evaluation of the immune properties of MPL *in vivo* and *in vitro*, immunogenicity studies to evaluate the adjuvant properties of MPL and aluminum hydroxide in mice, and a dose ranging study to look at immunogenicity of vaccine plus and minus the AS04 adjuvant in mice and monkeys. Results from these studies show that the AS04 adjuvant plays an important role in the activation of the innate immune response as measured in immunized mice and in cell based assays. In addition, the immune responses measured in animals inoculated with vaccine plus and minus adjuvant show a significantly enhanced response to vaccine formulated with MPL over vaccine adjuvanted with aluminum hydroxide or vaccine comprised of antigen only. The results from these studies support the use of the AS04 adjuvant system with this vaccine.

Summary of studies performed using final product vaccine: Four repeated-dose toxicity studies on the HPV-16/18 L1 VLP AS04 vaccine were carried out in rabbits and one in rats. These studies showed that the vaccine and adjuvant were well tolerated, and no consistent signs of systemic toxicity were observed. Injection site inflammation remained

local and showed signs of resolution. Up to three times the full human vaccine dosage was used in these toxicity studies, possibly increasing this local reaction. In addition, safety pharmacology studies were performed on HPV-16/18 L1 VLP AS04. The intramuscular administration of 1/5 of human dose of final container vaccine or the intravenous administration of ascending MPL doses up to 100 µg/kg bodyweight (50-100 fold the human dose of MPL in the AS04 adjuvant) showed no treatment-related effects on any recorded cardiovascular or respiratory parameters.

Summary of studies performed on MPL only: Results from preclinical toxicology studies conducted to detect potential toxicities associated with administration of MPL alone were submitted by GSK as part of the preclinical safety assessment program conducted to support the evaluation and licensing requirements for CERVARIX. Toxicology studies carried out to detect potential toxicities associated with administration of MPL alone included a single-dose toxicity study, repeated-dose toxicity studies, genotoxicity studies, embryofetal toxicity studies, and a pre/post-natal reproductive toxicity study. The final study reports from single- and repeat-dose toxicity studies conducted with MPL (alone) were submitted to the BLA. Overall, the data in these reports indicate that MPL adsorbed to aluminum hydroxide, as it exists in CERVARIX is suitable as a human vaccine adjuvant at the proposed dosage and formulation, as it demonstrates an acceptable safety margin, especially when administered by the proposed route of administration and dosing regimen.

Summary of Reproductive toxicity studies: It is important to note that although this vaccine is not intended for use in pregnant women, it is possible that women receiving this vaccine may become pregnant; therefore toxicity studies related to reproduction were also conducted. These studies included using the vaccine in a pre- and post-natal toxicity study in rats, which included an assessment of fertility. In addition, the safety profile of MPL, related to reproductive function, was examined in genotoxicity tests, embryo fetal toxicity studies in rabbits and rats, and a pre- and post-natal development toxicity study in the rat.

The conclusions from the reproductive toxicity study performed using CERVARIX were that there were no overt signs of treatment related maternal toxicity. Treatment did not affect body weights and body weight gains of the F0 generation neither did it affect body weight gain of the F1 generation born to treated dams. CERVARIX did not affect F0 female fertility, mating performance, embryo-fetal development and postnatal development. There were no observed treatment related effects on the incidence of major and minor abnormalities and skeletal variants in the offspring of dams treated with the test article except for two observations of small membranous intraventricular septal defect (IVSD). This defect was also identified in the reproductive toxicology studies performed in rabbits using MPL only. The association of this product containing AS04 and the development of IVSD was discussed with the sponsor and was included as an item in the CR letter . The sponsor responded to CBER in a satisfactory manner and it was concluded that the sponsor had adequately addressed the concern for a potential association between this product and the development of IVSD. The reviewer stated that no further risk management plan to assess the observation of IVSD is necessary. In addition, the final conclusion of the reproductive toxicology review was that, based on the results from

reproduction toxicity studies performed, pregnancy category B should considered for this product.

In conclusion, the pharmacology and toxicology studies performed in dogs, rabbits and rats showed that CERVARIX induces a strong and persistent specific immune response and is safe in animal models. CERVARIX did not demonstrate signs of systemic toxicity. The only conclusive effects seen were local and transient, and are expected from formulations that induce recruitment of inflammatory cells. Induced injection site reactions were the sign of the immune response generated against the vaccine antigens and enhanced by the adjuvant. These studies support the utilization of CERVARIX for human vaccination against HPV infections.

5. Clinical Pharmacology

The mode of action of this vaccine is to induce a specific immune response that will protect against disease after subsequent exposure to human papillomavirus. The immune response is measured by assaying for the presence of HPV type specific antibodies in the serum of vaccinated individuals. While immune response was measured in clinical studies, a correlation between antibody levels and clinical efficacy has not been established.

Preclinical studies, summarized in Section 4 of this document, were conducted to evaluate the immunostimulatory activity of the vaccine adjuvant, AS04, which is MPL adsorbed to aluminum hydroxide. Results from these studies demonstrate that the mode of action of the adjuvant is to stimulate the innate immune system and that the presence of the adjuvant provides a measurable enhancement to the immune response.

6. Clinical/ Statistical

Results discussed in this section are based on both the clinical and statistical reviews submitted to the file. The clinical studies conducted to demonstrate the efficacy and safety of this product, and to support the licensure of this vaccine, involved ~30,000 females 10 through 55 years of age, enrolled in 13 different clinical trials. Each study protocol and study outcome is detailed in the BLA and are covered in the clinical review. Critical studies to support the immunogenicity, efficacy and safety are also covered in the statistical review. It was the conclusion of both reviewers that the data presented support the recommendation for approval of this vaccine. Included in this memo is a summary of the critical findings of the clinical and statistical reviewers for the pivotal efficacy and safety studies (summarized in section 7 of this memo).

a) Clinical Program -

Efficacy – The pivotal efficacy study, HPV-008, was a randomized (1:1), controlled, double blind trial which recruited 18,000+ women 15 through 25 years of age, regardless of cytology status or evidence of HPV exposure. The study was designed to compare CERVARIX with an active control (Havrix – a vaccine to prevent hepatitis A) for the prevention of CIN2+, defined as a composite endpoint of CIN 2, 3, AIS and invasive

cervical cancer. In the According to Protocol population, efficacy against HPV 16 and HPV 18 associated CIN2+ was 92.9%, with 96.1%CI (79.9, 98.3). No subjects in either CERVARIX or the control group developed invasive cervical cancer during the study. Vaccine efficacy in study participants who had previous exposure to either HPV type present in the vaccine was reduced, showing that the vaccine does not function as a therapeutic vaccine. In addition, a prophylactic efficacy study, HPV 001/007, was conducted in an HPV naïve population (defined as PCR negative for 14 oncogenic HPV types, sero-negative for HPV 16/18, and cytology normal at baseline). In this study, 1,113 females 15-25 years of age were randomized to CERVARIX or aluminum hydroxide control. The estimate of efficacy for the primary endpoint of incident infection with HPV 16/18 in the ATP cohort was 92.6% (95% CI: 64.5, 98%).

Efficacy in 10 to 14 Year Old Females – The pivotal efficacy studies for this vaccine were conducted in females 15 through 25 years of age; however approval for this vaccine is sought for use in females from 10 through 25 years of age. The incidence of CIN2+ is very low among females younger than 15 years therefore it is not possible to demonstrate efficacy of this product for the requested disease endpoints. Therefore the immune response of females 10 through 14 years of age following administration of CERVARIX was compared with the response of participants in the pivotal efficacy studies. Efficacy was inferred by a demonstration of non-inferiority of the response (seropositivity rate and geometric mean titers) of females 10 through 14 years of age as compared to the response of females 15 through 25 years of age. These data support the use of this vaccine in younger females.

Prevention of Disease Caused by Non-Vaccine HPV Types - To determine whether CERVARIX has an effect on disease caused by non-vaccine HPV types, study HPV-008 included a secondary objective which measured a composite endpoint of prevention of CIN2+ associated with the following oncogenic HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. In this analysis the efficacy estimate in the According to Protocol (ATP) cohort was 54.0% (96.1% CI: 34.0, 68.4). It was difficult to determine the contribution of HPV 16 and/or HPV 18 to this result as these two types have a substantial impact on the composite endpoint analysis. The best estimate of the impact on non-vaccine types comes from a *post hoc* analysis in which HPV 16 and HPV 18 were excluded. Based on this type of analysis, the point estimate for efficacy in the prevention of CIN2+ associated with the remaining 12 oncogenic HPV types in the ATP cohort was 37.4% (96.1% CI: 7.4, 58.2). Determining the contribution of each non-vaccine HPV types in the prevention of histopathologically confirmed disease as identified in this analysis is complex. The statistical approach taken at CBER was to exclude co-infections with HPV 16 and/or 18, adjust for multiplicity, and estimate efficacy in the prevention of CIN2+ for each non-vaccine type individually. In this analysis, prevention of CIN2+ associated with HPV 31 was statistically significant in both the ATP and TVC naïve cohorts, with estimates of efficacy of 89.4% (99.7%CI: 29.0, 99.7%) and 100% (99.7%%CI: 36.3, 100%), respectively. Estimates of efficacy for the other 11 non-vaccine HPV types tested when HPV 16 and/or HPV 18 containing lesions were excluded from the analysis, did not reach statistical significance. Based on these analyses, it was determined that a composite end point for all non-vaccine types would not be allowed, however the

data for HPV31 was considered supportive and that information on this type could be included in the product label. This was discussed at the Vaccines and Related Biological Products Advisory Committee Meeting, held September 9, 2009 as part of the discussions related to the product label.

Summary points related to product efficacy:
The according to protocol (ATP) cohort for efficacy analyses for HPV 16 and/or HPV 18 included all subjects who received 3 doses of vaccine, for whom efficacy endpoint measures were available and who were HPV 16 and/or HPV 18 DNA negative and seronegative at baseline and HPV 16 and/or HPV 18 DNA negative at month 6 for the HPV type considered in the analysis. Case counting for the ATP cohort started on day 1 after the third dose of vaccine.

- The primary objective of the study, was prevention of CIN2+ lesions associated with HPV 16 or HPV 18. Cervarix was efficacious in the prevention of such lesions (92.9% [96.1% CI: 79.9, 98.3], $p<0.0001$) in subjects who were HPV 16 and HPV 18 sero-negative at baseline and HPV 16 and HPV 18 DNA negative at baseline and Month 6.
- In this population efficacy of CERVARIX to prevent CIN1+ lesions associated with HPV16 and HPV 18 was 91.7 % (96.1% CI 82.4, 96.7).
- In this population efficacy of CERVARIX to prevent CIN3 or AIS associated with HPV16 and HPV 18 was 80.0% [96.1% CI: 0.3, 98.1]).

Other Selected Analyses of Clinical data:

- In the ATP cohort, CERVARIX reduced the incidence of 12-month persistent infection with HPV 16 and/or HPV 18 by 91.2% (96.1% CI: 85.9, 94.8).
- Among subjects who received 3 doses of CERVARIX and who were seropositive at baseline and DNA negative for HPV 16 or HPV 18 at baseline and month 6, CERVARIX reduced the incidence of 12-month persistent infection by 91.5% (96.1% CI: 64.0, 99.2%). However, the number of cases of CIN2/3 or AIS was too few to determine efficacy against histopathological endpoints in this population.

Duration of Efficacy -The duration of efficacy has not been determined and it is not yet clear whether booster doses will be necessary. Data from the long term immunogenicity study shows that titers for anti- HPV16 and HPV 18 antibodies are well above the natural infection level at each time point considered. The sponsor is conducting several long-term follow-up studies (one a further extension of study HPV-001/007) to provide additional data regarding the duration of clinical efficacy of the vaccine.

In study HPV 001/007, the incidence of 6- and 12-month persistent infection and CIN2+ were assessed in subjects up to 6.4 years after vaccination. Among subjects HPV naïve at baseline CERVARIX prevented HPV 16/18 associated 6-month persistent infection (VE =100% [98.7%CI 86.2, 100]); 12-month persistent infection (VE = 100% [98.7%CI 74.4, 100]); and CIN2+ (VE =100% [98.7%CI 28.4, 100]).

Results of Bioresearch Monitoring Review – The BIMO reviewers conducted inspections of three clinical trial sites. These inspections were classified as voluntary action indicated and no issues were identified that would impact the clinical data submitted to the BLA to support licensure. One clinical trial site initially involved in the clinical studies was dropped from the studies due to non compliance with the study protocol. This action did not affect the outcome of the clinical trials. Overall, the conclusion from the BIMO report is that all studies reviewed were conducted according to study protocol and all data can be considered supportive of licensure.

b) Pediatrics – A presentation was made to the FDA Pediatric Research Committee (PERC) on July 8, 2009. The following recommendations were presented and accepted by the committee, and are included in the approval letter as follows:

> We are deferring submission of your pediatric study for CERVARIX, in females 9 years of age, until June 30, 2010, because the data support approval of this product for use in females 10 through 25 years of age, and this pediatric study has not been completed.
>
> Your deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.70 and Section 505B(a)(3)(B) of the FDCA. This required study is listed below:
>
> A clinical study to evaluate the safety and immunogenicity of GlaxoSmithKline Biologicals' Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant when administered to healthy females 9 through 25 years of age.
>
> We acknowledge your September 16, 2009, commitment to submit the final clinical study report by June 30, 2010.
>
> Please submit the final clinical study report to this BLA (STN 125259). For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated **"Required Pediatric Assessment."**
>
> We are waiving the pediatric study requirement for children from 0 through 8 years of age because the necessary studies are impossible or highly impracticable as there are too few children with the disease/condition to study.
>
> We note that you have fulfilled the pediatric study requirement for children 10 through 16 years of age with this application.

7. Safety

Safety data were collected from approximately 30,000 females, 10 through 72 years of age, in nine clinical studies. Study participants received at least one dose of CERVARIX or one dose of control vaccine (Havrix or aluminum hydroxide only). Adverse events were

reported and analyzed in several different categories. For non-serious adverse events, injection site reactions were noted more often for trial participants receiving CERVARIX over the controls. Other general adverse events noted within seven days of dosing and unsolicited adverse events, collected over a 30 day period, had rates that were comparable across all treatment groups.

Serious Adverse Events: In the CR letter, CBER requested a summary of serious adverse events (SAEs) across studies by treatment groups. In the pooled safety database, inclusive of controlled and uncontrolled studies which enrolled females 10 through 72 years of age, 5.3% (862/16,142) of subjects who received CERVARIX and 5.9% (814/13,811) of subjects who received control vaccine reported at least one SAE, without regard to causality, during the entire follow-up period (up to 7.4 years). In the vaccination period (Month 0 to Month 6), 1.3% of subjects in each group (206/16,142 CERVARIX recipients and 180/13,811 control subjects) reported an SAE. Among females 10 through 25 years of age enrolled in these clinical studies 6.4% of subjects who received CERVARIX and 7.2% of subjects who received the control vaccine reported at least one SAE during the entire study period (up to 7.4 years). There was no imbalance in the proportions of subjects who experienced an SAE across studies. In review of SAEs by System Organ Classification, there was no apparent imbalance between the CERVARIX and control groups.

Adverse Events/Serious Adverse Events leading to discontinuation from studies: In the CR letter, CBER requested a summary of adverse events (AEs) which led to discontinuation in the study. From a total of 29,953 subjects included in the pooled safety analysis, 72 subjects were withdrawn due to an AE or SAE (43 subjects received CERVARIX [0.27%] and 29 subjects received control [0.21%]). Thirty one of these subjects withdrew due to an SAE (14 subjects received CERVARIX [0.09%] and 17 subjects received control vaccine [0.12%]). Sixteen of thirty one events were fatal events. None of the deaths were assessed as related to vaccine administration. The other 15 subjects withdrew due to other SAEs, none of which were assessed as causally related to vaccination by the study investigator. In addition, there were 41 other subjects who experienced non-SAEs and withdrew from the study. Twenty nine subjects received CERVARIX (0.18%) and 12 subjects received control vaccine (0.09%).

AEs related to autoimmune events: At the time of the original BLA submission, several adverse events, including myelitis, disease related to demyelination, and optic neuritis, were detailed in the submission. In order to assess whether there was an increased risk of neuroinflammatory events after use of the vaccine, CBER requested that GSK provide a meta-analysis across controlled studies comparing MPL-containing products and non-MPL containing products. The meta-analysis was discussed with CBER statisticians to ensure proper methodology. The relative risk for neuroinflammatory events was determined to be 2.33; however this value did not reach statistical significance (95% CI: 0.53, 13.97). GSK also submitted a review of potential neuroinflammatory events identified in the meta-analysis conducted by an outside expert panel. This panel concluded there was not an increased risk of neuroinflammatory disorders following vaccination with MPL-containing products. In parallel, CBER requested a consultation from an outside neurologist with

expertise in neuroinflammatory diseases. The expert concluded that, in her opinion, the time from vaccination to event (within 12 weeks) must be taken into consideration in order for there to be a plausible link between vaccination and any neuroinflammatory event. Overall, the expert concluded that the data were insufficient to establish a link between vaccination and any neuroinflammatory event, although sufficient to raise a concern.

To ensure that the novel adjuvant, AS04, did not pose additional safety concerns the sponsor was asked to submit information regarding neuroinflammatory and autoimmune events associated with vaccine use. The sponsor submitted information on the following events:

- New Onset Chronic Diseases
- New Onset Autoimmune Diseases
- Neuroinflammatory Events
- Potential Autoimmune Disease in Musculoskeletal System Organ Class
- Grave's Disease

While there were incidences of these events in trial participants, the numbers were low and there was no imbalance identified in the occurrence of these events in either treatment group. The review team requested that the VRBPAC comment on the association of the vaccine with these adverse events. The VRBPAC acknowledged that there were no obvious issues related to the use of CERVARIX with these events, but did recommend related postmarketing studies. To continue follow up on this class of diseases the sponsor has committed to perform a phase IV study to assess neuroinflammatory autoimmune disease events in vaccinees. See section 11 of this report for a detailed description of this postmarketing commitment.

Pregnancy outcomes: Overall, the pregnancy outcomes measured between the CERVARIX and control groups were similar. However, it was noted that in a post-hoc subgroup analysis that there was an imbalance in the rate of spontaneous abortions between the CERVARIX and the Havrix control groups; with a higher incidence of spontaneous abortions seen in the CERVARIX group when pregnancy occurred around the time of vaccination. Women were advised against pregnancy during these clinical studies; however there were a number of pregnancies in both CERVARIX and control groups. Of the identified pregnancies, 2.0% and 2.1% the pregnancies that occurred in the CERVARIX and control groups, respectively, had an estimated date of conception within -30 to +45 days of vaccination. In this risk window in the 15 through 25 year old subjects, 13.51% for CERVARIX, 8.33% for aluminum hydroxide, and 8.92% for Havrix control of documented pregnancies ended in spontaneous abortions. In females > 25 years of age, the proportions of women reporting spontaneous abortion were similar for CERVARIX (19.05%) and the aluminum hydroxide control (20.0%).

The following limitations to assessing spontaneous abortion rates in this situation were noted: (1) the studies were not designed to assess the possible effects on pregnancy; (2) spontaneous abortion was not a pre-specified outcome and therefore the clinical trials were not designed to study spontaneous abortion; (3) the choice of risk window was not pre-specified; (4) the imbalance at issue was largely among subjects who became pregnant *after they were vaccinated;* very few subjects with established pregnancies were actually

vaccinated because each subject received a urine HCG (pregnancy test) the day of vaccination, and if positive, vaccination was deferred; (5) the rate of spontaneous abortion in each group, including the CERVARIX group, was consistent with background rates reported in the literature (9-21%); (6) in pregnancies which occurred around the time of vaccination, there was no difference in the mean time to spontaneous abortion in each group; and (7) pre-clinical reproductive toxicology studies did not identify any increase in risk.

To further address the potential association of spontaneous abortion rates and vaccination with CERVARIX, an independent analysis was conducted by the National Cancer Institute (NCI). After completing the analysis, the statistician could neither refute nor confirm an increased rate in spontaneous abortion among vaccine recipients. In addition, an Independent Data Monitoring Committee found no evidence for causal association between HPV vaccine and spontaneous abortion, but could not exclude a possible association between HPV vaccine and spontaneous abortions in the first 90 days after vaccination and onset of pregnancy. CBER concluded that the imbalance in rates of spontaneous abortions met regulatory criteria for a safety signal. Therefore, GSK will be required to conduct a post-marketing study to evaluate pregnancy outcomes, particularly spontaneous abortions. This study is detailed in Section 11 below.

8. Advisory Committee Meeting

A meeting of the VRBPAC was held on September 9, 2009. The following questions were presented to the committee for consideration:

1. (A) Do the data support the efficacy of CERVARIX for the prevention of HPV 16/18 related cervical cancer, CIN2+, AIS, and CIN1+ in females 15-25 years of age?

   (B) Do the immunogenicity bridging data support effectiveness for prevention of HPV 16/18 related cervical cancer, CIN2+, AIS, and CIN1+ in adolescent females 10-14 years of age?
2. Please comment on the strength of the data to support the efficacy of CERVARIX for the prevention of any non-vaccine HPV related CIN+ in females 10-25 years of age.
3. Do the safety data support the safety of CERVARIX for use in females 10-25 years of age?
   a. Please comment on imbalance noted in spontaneous abortions in 15-25 year old females around the time of vaccination.
   b. Please comment on findings for neuroinflammatory events and diseases of potential autoimmune etiology.
4. Please comment on other recommendations for postmarketing commitments.

The committee was asked to vote on items 1A and 1B and 3. The other items were discussion items.

Regarding questions 1A and 1B, the committee felt that the clinical data supported the efficacy of CERVARIX to prevent HPV 16 and HPV 18 related cervical cancer and precancerous lesions CIN and AIS in females 15-25 years of age, and that immunogenicity data, used as a bridge to efficacy, support effectiveness for prevention of HPV 16/18 related cervical cancer and precancerous lesions CIN and AIS in adolescent females 10-14 years of age. The votes for both 1A and 1B were **12** yes, **1** no, **0** abstain.

Regarding question 3, related to the safety of the vaccine, the committee felt that while the safety issues discussed, specifically issues related to the imbalance in spontaneous abortions and the potential for neuroinflammatory events and diseases of potential autoimmune etiology were important and should be followed in postmarketing studies, the safety data presented both by CBER and by the sponsor confirmed and supported the stated safety of the product. The votes for question 3 were **11** yes, **1** no, **0** abstain.

The committee was also asked to comment on the strength of the data supporting efficacy in prevention of non-vaccine HPV types. The chairperson summarized the discussions by indicating that there was good basis of concluding that this bivalent vaccine does protect against some non-vaccine serotypes, most likely those to which there has been demonstrated cross protection in animal models or cross neutralization, but that they were uncomfortable with the term "any non-vaccine HPV type". There was some difference of opinion as to whether there was need to be any more specific than that with regard to specific types, particularly HPV-31. Caution was also advised in interpreting the data related to non-vaccine types due to assays used and their ability to differentiate between non-vaccine HPV types.

9. Other Relevant Regulatory Issues

No other significant regulatory issues were identified during the review of this file.

10. Labeling

The package insert (PI) originally submitted to the BLA and all subsequent amendments related to the label were reviewed by all relevant reviewers on the file. Several rounds of changes were made to the label submitted by the sponsor. Many of these changes were minor; however several critical changes were made. These included removing indications related to the prevention of HPV 16 and HPV 18 infection, both incident and persistent infection, and indications related to the prevention of abnormal cytology associated with HPV 16 and HPV 18. In addition, changes in the data presented on the effectiveness of CERVARIX to protect against HPV types not present in the vaccine were removed from the label. Extensive discussion occurred internally, and with the sponsor, regarding the data submitted to support an indication for the prevention of disease caused by HPV types not included in the vaccine. The advisory committee was asked to comment on the data presented on the inclusion of data on protection conferred for non-vaccine HPV types. The advisory committee acknowledged that the data was supportive; however it was not statistically significant for the majority of non-vaccine types studied. An agreement was reached between CBER and the sponsor that the data to support cross protection with HPV type 31 was statistically significant and therefore this data is included in the Description section of the label.

Based on the reproductive toxicology studies and the safety data from the clinical trials related to pregnancy events, the label will have a statement that this product is classified as Pregnancy Category B. The label will also state that safety has not been established in pregnant women and that this product is not intended for use in pregnant women, or women who plan on becoming pregnant during the time of vaccination.

In addition to the package insert, the Advertising and Promotional Labeling Branch reviewed, and found acceptable, the proposed proprietary name for this product, the vial, carton and container packaging information, and the logo and pre-product release advertising. After some discussion with the sponsor, all of these submissions were found to be acceptable.

The sponsor will submit the label in Structured Product Labeling format after product licensure.

11. Recommendations and Risk/ Benefit Assessment

a)Recommended Regulatory Action
Following the review of all supportive product and clinical data, it is the recommendation of the review committee to approve this product for licensure.

b) Risk/ Benefit Assessment
The quality, efficacy, and safety of this vaccine have been thoroughly reviewed and have been determined to be acceptable for use of this vaccine as indicated in the label. The benefits from using this vaccine are related to the high efficacy for the prevention of cervical cancer as demonstrated in the results of the clinical studies.

c) Recommendation for Postmarketing Risk Management Activities
There was no recommendation for postmarketing risk management activities. See below for the postmarketing activities associated with the licensure of this product.

d) Recommendation for Postmarketing Activities – Postmarketing activities include studies that will be performed post-licensure. These studies are classified as either postmarketing requirements under Section 505(o) of the Food Drug and Cosmetic Act (FDCA), postmarketing commitments subject to 21 CFR 21 601.70. or postmarketing commitments not subject to 21 CFR 601.70. During the review of the BLA it was determined that a postmarketing requirement study related to assess the relative risk of spontaneous abortion associated with vaccination around the time of conception. The plan and timing for this study was discussed with GSK and an agreement was reached on how the study was to be conducted.

Two additional postmarketing studies to follow product safety were discussed with GSK. These include a study to monitor autoimmune associated AEs and the establishment of a

pregnancy registry. One postmarketing commitment to submit final study reports for ongoing clinical endpoint efficacy studies. Two CMC related PMCs to assess product stability were also requested.

The sponsor agreed to all studies and will submit reports as requested. These commitments are included in the approval letter.