



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20852-1448

Our STN: BL 125259/0

GLAXOSMITHKLINE BIOLOGICALS

Attention: Sharon W. Shapowal, R.Ph.  
2301 Renaissance Blvd, Building 510  
King of Prussia, PA

**DEC 14 2007**

Dear Ms. Shapowal:

We have completed the review of your submissions dated through December 12, 2007, to your biologics license application (BLA) for Human Papillomavirus Vaccine, AS04 Adjuvant-Adsorbed (Cervarix) submitted under section 351 of the Public Health Service Act.

We acknowledge receipt of your amendment dated December 13, 2007. You may cross reference applicable sections of the amendment in your complete response to this letter and we will review those sections as a part of your complete response.

The deficiencies are as follows:

CLINICAL/ STATISTICAL

Interim clinical efficacy data and blinded safety data were accepted for filing of your application as evidence of effectiveness and safety, respectively; however, when analyzed, CBER is unable to assess the benefits and risk of your product because both safety and efficacy data are deficient. Final efficacy data from your pivotal Phase 3 studies and unblinded safety data are needed for our complete assessment of this application. Furthermore, our evaluation of your interim data raises the following concerns:

Safety

1. Your product contains both HPV Virus Like Particles Adsorbed and AS04 adjuvant, added to enhance the immune response to the HPV vaccine antigens. We have determined from our review that there are numerical imbalances for neuroinflammatory adverse events and potential autoimmune musculoskeletal events in the two treatment groups (vaccine vs. control), and potentially other adverse events. Given the imbalances observed in subjects who received Cervarix compared to those receiving controls, we are concerned about the possibility that these imbalances may be due to the adjuvant. Under 21 CFR 610.15(a), an adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety of the product. Please describe how you will address this requirement.

2. At the time of the pre-BLA meeting, CBER raised the issue of presentation of blinded safety data, and stated that the Agency needed to ensure that adverse events could be readily identified and easily reviewable in the BLA (CBER minutes from pre-BLA meeting, May 1, 2006). GSK assured that all adverse events would be displayed by treatment group and by preferred term, and that the FDA could request any adverse event (AE) data not listed through the firewall group (GSK minutes of pre-BLA meeting, May 1, 2006; IND (b)(4), Amendment 247, Serial 248). However, we are unable to complete our assessment of the safety of Cervarix because the data were presented incompletely in a blinded manner. Additionally, regarding the deaths reported in the BLA, we note the following:

- In the summary of safety data section of the BLA (Module 2.7.4 Summary of Clinical Safety) five deaths in Study HPV-008 were reported up to the data lock point of September 30, 2006 (p. 103).
- Two additional deaths were reported to IND (b)(4) (one in Study HPV-008 and one death in Study HPV-009) which were possibly related to HPV 16/18 vaccine. We note that only one of these deaths (Subject 389954) was included in the section discussing deaths in ongoing trials (Module 2.7.4 Summary of Clinical Safety, Section 2.1.2.2, pp. 104-105.) Details regarding the other subject in Study HPV-008 (Subject 71903) were included in the section of Serious Adverse Events (SAEs) considered to be related or possibly related to vaccination (Module 2.7.4 Summary of Clinical Safety, Section 2.1.3.5, p. 132), but the information provided did not include the fact that this subject had died. We acknowledge that this death occurred in February, 2007, which was after the data lock point. However, this was still > 1 month prior to the submission of the BLA and the death of this subject should have been reported in the BLA and included in the total deaths that occurred in Cervarix studies.
- We note that several other deaths were included in the section on deaths in ongoing studies (Study HPV-009) (Module 2.7.4 Summary of Clinical Safety, Section 2.1.2.2, p. 103) and treatment allocation information was provided for four of five of these reported deaths upon request.
- We also note that in a recent presentation at the ACIP meeting (October 25, 2007), the five deaths noted within the Summary of Clinical Safety for Study HPV-008 (Module 2.7.4 Summary of Clinical Safety, Section 2.1.2.1, pp. 102-103) were the only ones included.

Specifically, we have the following comments:

- a. In view of the information noted above, we request that you provide an updated presentation of the deaths that have occurred in clinical studies of Cervarix, including Study HPV-009. We request that you provide information regarding all deaths regardless of attribution (i.e., even if the death was not considered to be vaccine-related by the investigator.). We request that you provide one comprehensive table listing all deaths as of September 30, 2007, and include information regarding treatment allocation, time to event relative to vaccination, and investigator attribution in each case.

- b. We note that Serious Adverse Events (SAEs) reported as possibly related to vaccination by investigators up to the data lock point of September 30, 2006, are presented in Table 42 of the Summary of Clinical Safety. This list is difficult to read, and although most events have been unblinded, there are several that remain blinded. We request that you provide an updated table of such events through September 30, 2007. The information should be presented by diagnosis, treatment allocation, time to event, and outcome. Diagnoses should be grouped by System Organ Classes (SOC) group. Please use the table below as a guide on how to present the adverse event data.

**SAEs in Studies HPV-001/007, 008, 012, 013, 014, 015, 016 through 9/30/07**

| Event/Severity/<br>History or<br>Family<br>history/age | PID/Country/<br>Study | Days postdose/<br>Recovered/Related | Event/Severity/<br>History or<br>Family<br>history/age | PID/Country/<br>Study | Days postdose/<br>Recovered/Related |
|--|-----------------------|-------------------------------------|--|-----------------------|-------------------------------------|
| Cervarix   |                       |                                     | Control  |                       |                                     |
|  |                       |                                     |  |                       |                                     |
|  |                       |                                     |  |                       |                                     |

- c. Please provide an updated table of pregnancy outcomes through September 30, 2007, including information from studies 001/007, 008, 009, 012, 013, 014, 015, 016. Specifically we have the following comments and requests:
- The reported rates of spontaneous abortion are higher in the HPV vaccine group as compared to the HAV (control) group in Study HPV-008. You claim that the rates in both groups are lower than those reported in US epidemiological studies of spontaneous fetal losses from recognized pregnancies (13-16%). It should be noted that “fetal loss” includes live births, stillbirths, spontaneous abortions (including hydatidiform mole), and ectopic pregnancies. As shown in one of the publications which you cited (Goldhaber, 1991), “Omitting ectopic pregnancies decreased the estimate (rate of spontaneous abortions) to 11.9%.” Therefore, the reported rates of spontaneous abortion may in fact be similar or even higher than those in US epidemiological studies. Please comment.
  - If the outcome was a spontaneous abortion, information regarding estimated time to conception (either prior to or after vaccination), attribution, treatment group and description of event should be included.
  - Since an imbalance in the proportion of subjects with a spontaneous abortion from -30 to +45 days was noted for all studies included in the pooled safety dataset, we request that data from Study HPV-009 also be included in the updated table of pregnancy outcomes. We suggest that you use unblinded Tables 58 (p. 178) and 60 (p. 176) within Module 2.7.4, Summary of Clinical Safety, as guides for how the data in the updated table should be presented.

- iv. Given the imbalance in the number of stillbirths noted for the pooled data, we request that you include the number of stillbirths that occurred within Study HPV-009. We note that two stillbirths were reported in a blinded table from Study HPV-009. For each reported stillbirth, please provide information on the treatment group, time from vaccination to estimated date of conception, and time to event.
- d. Regarding pregnancies with abnormal infant outcomes, we note the following:
- There was a neonate with a ventricular septal defect (VSD) whose mother participated in Study HPV-009 and received dose 2 of Cervarix approximately five weeks prior to her last menstrual period (LMP). We acknowledge that a second neonate whose mother received aluminum hydroxide also developed a ventricular septal defect, but the time interval between vaccination and estimated date of conception was 714 days, and temporal association in this second case is not apparent.
  - Increased rates of similar defects were reported in animal developmental toxicology reports for MPL.
  - Two other neonates born to mothers who received Cervarix in Study HPV-009 were not included in the unblinded version of Table 59. One neonate born to subject 42608 had laryngomalacia (p. 128 of Summary of Clinical Safety) and the second neonate born to subject 470854 had hip dysplasia. Other congenital defects were identified in the review (e.g., the infant with Apert's syndrome born to subject 376871 whose mother received Havrix) but were not included in the summary table.
  - In total, 35 congenital anomalies were noted in a blinded table for pregnancy outcomes for Study HPV-009.
- i. We request that you provide an updated presentation of pregnancies with abnormal infant outcomes through September 30, 2007. This table should include infants born to mothers participating in Study HPV-009. The study in which the abnormality was noted should be specified. Information regarding treatment allocation and events should be prepared by an unblinded statistician and submitted to CBER for review. Additionally, we request that you submit any International Event Reports for such congenital anomalies. We recommend that you use the table provided below as a guide.

**Description of abnormal infant outcomes**  
**(Studies 001/007, 008, 009, 012, 013, 014, 015, 016)**

| Treatment /Study Number | Case ID /Subject ID mother | Gender | Age     | Event                           | Time from last vaccination to conception (days) | Time from last vaccination to diagnosis (days) |
|-------------------------|----------------------------|--------|---------|---------------------------------|---|--|
| HPV /Study ----         | B0265093B /-----           | Female | Neonate | Talipes equinovarus, congenital | 3   | 266  |
| HPV /Study-----         | B0402771B /-----           | Male   | Neonate | Atrial flutter                  | 1370  | -  |
| HPV /Study ----         | B0406847B /-----           | Female | Neonate | Meningomyelocele ,Hydrocephaly  | 197   | 483  |
| HAV                     |                            |        |         |                                 |   |  |
| ALU                     |                            |        |         |                                 |   |  |

- e. Please provide a list of discontinuations from study participation due to adverse events for all Phase 2b and Phase 3 studies (controlled and uncontrolled) which were submitted in support of licensure. We request that you provide this information in one table and include study number, PID number, event, time from vaccination to event, severity, attribution of event, and outcome. We recommend that these events be arranged by System Organ Classes (SOC) category. If data are available from Study HPV-009, we request that you include this information in the table also.
- f. Our review has identified neuroinflammatory events which were reported in clinical studies of GSK products and these are presented in Table A. In addition, another sponsor has shared with you information on a case of transverse myelitis in a Phase 3 trial involving an MPL-adjuvanted (b)(4) product. We have the following items:
  - i. Please clarify whether all cases of neuroinflammatory events to date for GSK's MPL-containing products (from both IND and non-IND studies) have been reported to CBER. If there are cases of neuroinflammatory events which have not been reported to CBER (e.g., cases which may have occurred more recently), we request that you submit this information to the Cervarix BLA and to the respective INDs.
  - ii. Please provide an overall assessment (rather than a case-by-case diagnostic interpretation) of neuroinflammatory events which occurred in clinical studies with GSK's MPL-containing products, including those presented in Table A. We also request that you provide a similar assessment of the musculoskeletal events listed in Table B below (includes Study HPV-009). These overall assessments should include the estimated background rates with which these events occur.

**Table A. Neuroinflammatory Events Identified Across GSK Studies in Products Containing MPL**

| MPL                  |   |  | Non-MPL   |                    |                             |
|----------------------|---|--|-----------|--------------------|-----------------------------|
| HPV studies          |   |  |           |                    |                             |
| Subject ID/Study     | Event   | Time to Event                              | Case ID   | Event              | Time to Event               |
| 704/Study 014        | Optic neuritis                                | 9 days postdose 1                          | 1658/010  | Multiple sclerosis | 60 days postdose 1 Gardasil |
| 1264/Study 014       | Multiple sclerosis                            | 25 days postdose 2                         | 11937/008 | Optic neuritis     | 134 days postdose 3         |
| 2030/study Tetra 051 | Myelitis                                      | 47 days postdose 2                         | 14111/008 | Optic neuritis     | 23 months postdose 3        |
| 0037/study 012       | Demyelinating disease                         | 129 days postdose 2                        |           |                    |                             |
| 1020/study 008       | Optic neuritis                                | 15 months postdose 3                       |           |                    |                             |
| 2475/008             | Optic neuritis and multiple sclerosis         | 17 months postdose 3                       |           |                    |                             |
| (b)(4) studies       |   |  |           |                    |                             |
| 1605.(b)(4) 016      | Encephalitis/MG/cellulitis                    | ? time after dose 1 and 10 days postdose 2 |           |                    |                             |
| 1435.(b)(4) 007      | MS (history of MS years prior to vaccination) | 8 months postdose 3                        |           |                    |                             |
| 3869 (b)(4) 017      | MS  | 7 months postdose 3                        |           |                    |                             |

**Table B. Potential Autoimmune Events in the Musculoskeletal SOC in Cervarix Studies (Includes cases requested from Study HPV-009)**

| Event, Severity/history or FHx/Age   |                   |                                    | Event, severity                           |                   |                                   |
|--|-------------------|------------------------------------|---|-------------------|-----------------------------------|
| Arthritis  |                   |                                    |   |                   |                                   |
| Cervarix   | PID/Country/Study | Days postdose/Rec/Rel/Ser*         | Control –Havrix or ALU                    | PID/Country/Study | Days postdose/Rec/Rel/Ser*        |
| Days 0-30  |                   |                                    | Days 0-30                                 |                   |                                   |
| **Arthritis, moderate/14 yrs (karate athlete, received 3 doses)                  | 1063/EST/014      | 1 day postdose 2x91 days/<br>1/N/N | **Arthritis, moderate/45 yrs (arthralgia) | 5471/MX/015       | 12 days postdose 2 x 1d/<br>1/N/N |
| TMJ arthritis, moderate/17 yrs (also with inc. LN and oral ulcer 4 M postdose 2) | 21505/TW/008      | 2 days postdose 2x164 d/<br>1/N/N  |   |                   |                                   |
| Knee inflammation, mild/19 yrs   | 7706/BRA/008      | 5 days postdose 3x7 d/<br>1/N/N    |   |                   |                                   |
| **Arthritis, severe (Arthralgia)/45 yrs (received 3 doses, also received MMR 2M  | 7141/PER/015      | 12 days postdose 1x4 d/<br>1/N/N   |   |                   |                                   |

|  |                       |                                     |  |                       |                                       |
|--|-----------------------|-------------------------------------|--|-----------------------|---------------------------------------|
| postdose 2)  |                       |                                     |  |                       |                                       |
| Fibromyalgia/22 years Within month of dose 2, c/o pain in wrists, shoulders and toes. Initially dx'd with RA; RF +; ANA + 1:40; Rx'd with NSAIDs and steroid; cardiolipin Ab weakly + 14.4; dx changed to fibromyalgia and rx changed to Tylenol, fluoxetine, and imipramine with improvement. | 482958/Costa Rica/009 | Within 30 days/2/NS/N               |  |                       |                                       |
| Days 31-60   |                       |                                     | Days 31-60   |                       |                                       |
| Fibromyalgia (hx of asthma, migraines)/36 years of age, developed joint pains, then 3 months postdose 2 dx'd with fibromyalgia*****  | 4593/_/015            | 43 days postdose 2                  |  |                       |                                       |
|  |                       |                                     | RA/25 years Pain in knees in elbows, wrists and fingers; +FHX RA; RF+1:16, CRP +. Dx'd with FRA, placed on prednisolone and Indocin. Improved on meds @8 mos after dx. | 216829/Costa Rica/009 | 60 days postdose 3/4/NS/N             |
| Days 61-90   |                       |                                     | Days 61-90   |                       |                                       |
| Reactive arthritis, severe/21 yrs (withdrew from study-arthritis wrist, feet)  | 160/_/016             | 63 days postdose 2/ 3/Y/N           |  |                       |                                       |
| Knee joint inflamed, mild/16 yrs (history asthma and allergies), received 3 doses  | 86676/FIN/008         | 66 days postdose 2x31 d/ 1/N/N      |  |                       |                                       |
| Fibromyalgia/21 years (history asthma, spastic colon) Treated with NSAIDs. Amitriptyline, prednisolone (tapering) and recovered, but maintained on meds  | 294498/Costa Rica/009 | 78 days postdose 2 x 1 year/1/N/Y   |  |                       |                                       |
| Days >90   |                       |                                     | Days > 90  |                       |                                       |
| Reactive arthritis, severe/24 yrs, did not receive dose 3 (resolved after 3 weeks, also with inc. LNs; states that inc. LNs recur with stress)   | 57/22352/014          | 106 days postdose 2x 3 weeks/ 1/Y/N | RA, moderate   | 7669/BRA/007          | 1234 days postdose 3 (chronic)/2/ N/N |
| Reactive arthritis, moderate/17 yrs, swollen ankle and knee (with inc. CRP – on MTX+Pred+Sulfa)  | 14118/FIN/008         | 112 days postdose 3/2/N/Y           |  |                       |                                       |

|  |              |  |  |  |  |
|--|--------------|--|--|--|--|
| **Knee joint inflammation, moderate/35 yrs (received 3 doses)  | 237/GER/014  | 126 days postdose 2x24 days/<br>1/N/N                          |  |  |  |
| **RA, moderate/22 yrs with hx asthma & allergies (sx started 3-4 months postdose 3, FHx + arthritis) | 11150/UK/008 | 194 days postdose 3x123 d/<br>4/ /N (causality being reviewed) |  |  |  |
| RA, moderate/25 yrs  | 8416/MX/008  | 269 days postdose 3x4 d/<br>1/N/Y                              |  |  |  |

\*Rec = recovery: 1= recovered; 2 = recovering; 3 = not recovered; 4= recovered with sequelae; 5=fatal;

Rel = related (Yes/No); Ser = Serious (Yes/No)

\*\*AEs not identified as AIDS by GSK but found within Musculoskeletal or Neuro unsolicited AEs;

\*\*\*\*\*Case added due to narrative request

- g. Please note that we are awaiting responses to requests for source documents available for subjects indicated to have experienced neuroinflammatory events and potentially autoimmune events in your Level 3 and Level 4 analyses (discussed during a teleconference between CBER and GSK on November 13, 2007). Please submit the source documents as soon as possible.
  - h. Please indicate if the case of multiple sclerosis reported in Study HPV-010 has been reported to VAERS.
  - i. We request that unblinded versions of all blinded safety tables be submitted to the BLA. Please respond.
3. Regarding the meta-analysis of results for MPL-containing products, results of the statistical test for homogeneity of the common relative risks of Grave's disease tend to be statistically significant in both Level 2 and Level 3 analyses. This evidence of lack of homogeneity of relative risks across studies suggests that the overall summary analysis results may be subject to bias. Thus, further careful review of the data for each individual study regarding the rates of Grave's disease may be warranted. Please comment.

#### Efficacy

4. In Study HPV-008, the primary endpoint is defined as "Histopathologically-confirmed CIN2+ associated with HPV-16 or HPV-18 cervical infection detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA)." Results of the interim analysis demonstrated that vaccine efficacy against CIN2+ associated with HPV 18 did not reach statistical significance (VE = 83.3% [-78.8%, 99.9%], p=0.1249). Please comment and explain how the data from this interim efficacy analysis supports an indication for both HPV 16 and 18-related CIN 2+ and cervical cancer prevention.



5. We would like to reiterate that CBER did not concur with the interim analysis success criterion of the lower 97.9% confidence limit excluding only zero. As communicated to you via fax (June 17, 2005) and confirmed in a telecon between CBER and GSK (June 28, 2005), CBER did not concur with a proposal for an interim analysis for Study HPV-008 in which the criterion for the lower bound of efficacy was 0%, and stated that it be substantially above 0% (e.g., 25-30%). In Amendment 151 (Serial 150) to IND (b)(4), the proposed clinical plan for licensure in the US, a  $LB \geq 25\%$  was cited by GSK as the lower bound criterion at the time of the interim analysis, and this was also acknowledged within the BLA in Module 2.5 Clinical Overview, Section 1.3.5, p. 78. Please restate your conclusion based on a lower bound of the 97.9% CI as  $\geq 25\%$ .
6. Regarding the difference in the analysis populations at the interim analysis and at the time of final analysis, the efficacy data submitted to support licensure in the prevention of HPV 16 and 18 related CIN 2+ were based on an interim analysis in the Total Vaccinated Cohort-1. In the Study HPV-008 Study Report (Synopsis, p. 2), it states: "Objective of the interim analysis: The current report describes the results of the interim analysis. For this analysis, efficacy objectives have been assessed post dose 1 in adolescent and young adult women who were DNA negative for the corresponding IIPV type at Month 0 with normal or low-grade cytology at baseline." A different population, the According to Protocol Cohort (ATP cohort), in which subjects who were seronegative at baseline and PCR negative through Month 6, will be used to assess efficacy at the time of the final analysis. We have the following comments:
  - a. Of the 23 cases of CIN 2+ used to provide demonstration of efficacy at the time of the interim analysis, 14 subjects became PCR positive for the relevant vaccine HPV type by Month 6 (including subjects 10076, 13452, 14290, 14386, 16973, 20287, 11942, 21724, 12104, 12692, 20838, 4249, 4451, 14079). These 14 cases counted at the time of the interim analysis should not be counted as cases at the time of the final analysis, given the different analysis populations. Please confirm.
  - b. The primary analysis of vaccine efficacy against IIPV 16 or 18 related CIN 2+ at the time of the interim analysis counted cases after dose 1. The indication for vaccine administration includes three doses of vaccine at 0, 1, and 6 months. The time to development of the 23 endpoint cases of CIN 2+ ranged from 8 months to 29 months, with a mean time to event of 15.9 months (median: 14 months), which is after administration of dose 3. Please explain how the difference in the population assessed at the time of interim analysis and final analysis will be reconciled with the recommendation for three doses of vaccine.
  - c. We note that 22/23 of the subjects who developed a CIN 2+ endpoint had received three doses, and the time to development of a case varies from 8 months to 29 months, i.e., after the time of the third dose. Moreover, nearly all subjects received three doses of study material in Study HPV-008. Thus, the data do not provide evidence that the vaccine has an early onset of effect. Please comment.

7. In Study HPV-008, for the evaluation of the candidate vaccine compared with control in the prevention of persistent infection (6-month definition) with the following oncogenic HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 (by PCR), there are 14 different secondary analyses and no adjustment for alpha has been considered. It is possible that a correlation between prevention of persistent and incident infection with CIN 2+ prevention may be demonstrated in the future, but the current data are not indicative of this. Furthermore, the current analyses related to persistent and incident infections lack adjustment and introduce considerable Type I error probability. The same comment applies to the evaluation of histopathologically-confirmed CIN1+ (or CIN2+) associated with the oncogenic HPV types detected within the lesional component of the cervical tissue specimen. Please comment.
8. In the Clinical Overview on p.41, you state that interim safety data and immune responses in women > 26 years of age provide evidence that Cervarix protects against CIN 2+ associated with HPV 16 or 18 in this older age group. Given the absence of efficacy data in this population against development of CIN 2+, the likelihood that older women are sexually experienced, the type-specific lack of efficacy in females with pre-existing HPV infections, and the incomplete information at the time of interim analysis from Study HPV-015 regarding the proportion of women who were non naïve at baseline, it remains unclear if Cervarix will prevent HPV 16 or 18 related CIN 2+ in this older age group. Please comment.
9. Since all Study HPV-001 and Study HPV-007 combined analyses were descriptive, CBER views them as exploratory and unlikely to support label claims. Please comment.

Other Clinical/Statistical Comments:

10. We note that no correlation between immunogenicity and vaccine efficacy has been identified in Studies HPV-008 and HPV-001/007. In particular, it is important to investigate the immunogenicity information of those CIN2+ cases associated with HPV-16/18. Please provide immunological data for CIN 2+ cases in the study group that received Cervarix.
11. Results of Studies HPV-012 and HPV-013 Ext. show that the immune response in 10-14 year old girls was sustained up to 18 months following vaccination. Please provide a plan of assessing the immune response beyond 18 months after vaccination in this age group. Please provide similar information for women 26 years of age and above.

TOXICOLOGY

12. As stated in our communication of August 31, 2007, it is not clear whether the finding of membranous ventricular septal defect observed in studies (b)(4) 249 and (b)(4) study 1729/8 –D6154 is a treatment related finding, since it is isolated (i.e., occurrence 1 fetus/litter/group and also observed in historical controls.) However, we remain concerned because in the reported studies this event was not observed in concurrent controls and furthermore, the incidence is high compared to historical controls (in Study (b)(4) 249: 0.6% by fetus and 4.5% by litter whereas historical background rates are 0.033% to 0.096% by

fetus or 0.235% to 0.683% by litter). The Table entitled “Terminology of developmental abnormalities in common laboratory mammals” Version 2, 2006, ([http://teratology.org/news\\_resources/DevToxTerms.htm](http://teratology.org/news_resources/DevToxTerms.htm)), published by the Teratology Society suggests that a defect in the membranous ventricular septum may be associated with Tetralogy of Fallot, a congenital heart defect. Furthermore, review of an adverse event observed in the ongoing clinical Study HPV-009 in Costa Rica in a 20 year old woman receiving dose 2 of Cervarix (3/15/05) approximately 5 weeks prior to her LMP (4/22/05) revealed a pregnancy outcome of an infant with a muscular ventricular septal defect assessed by the investigator as possibly related to study material in view of the temporal association between vaccination and estimated date of conception.

We acknowledge that VSD is reported to occur in 2-7% of human live births in the US and is considered a very common congenital anomaly that can resolve spontaneously. Furthermore, we note that the VSDs observed in Study (b)(4) 249 conducted in rats and (b)(4) Study 1729/8 –D6154 conducted in rabbits refer to the membranous septum and not to the muscular septum as observed in the pregnancy outcome in Study HPV-009. However, given the high incidence of ventricular septal defect in the reported developmental toxicity studies relative to concurrent and historical controls, and occurrence of this finding in more than one species, we request that you:

- a. Please comment on the potential association of ventricular septal defect with HPV/AS04 vaccine.
  - b. Please propose a risk assessment and risk management plan to address this observation.
13. With respect to Module 2.6.6., Toxicology Written Summary – MPL, Common Technical Document Summaries, it was noted in Module 2.6.6.3.1 (p. 5) that the summary discussion of the 8 day IV toxicity study in (b)(4) rats (Study (b)(4) 3262.2) included mention of the treatment-related mortality that occurred in the high dose level group (started at 5000 mcg/kg/day and then lowered to 2500 mcg/kg/day.) However, only those changes observed in rats from each MPL treatment group sacrificed at study termination were discussed in the summary of the test-article related microscopic changes. Please discuss in Module 2.6.6.3.1 the specific test article-related microscopic changes (i.e., edema or hemorrhage in brain and spinal cord) observed in the 3/20 rats that died or were sacrificed moribund during the study.

#### PHARMACOVIGILANCE

14. We acknowledge receipt of your amendment, describing the protocol for the post-marketing study in Scotland, dated December 13, 2007. If this amendment did not include background rates in Scotland for neuroinflammatory and autoimmune diseases (AIDs) please submit them as well. Depending on subsequent CBER evaluation and final labeling CBER may request additions to the Pharmacovigilance Plan.

CMC

15. Please submit the most current data for all samples currently on stability study.
16. With respect to the specifications for HPV final container vaccine, the specification for the test for (b)(4) MPL component has been set at (b)(4) of the nominal value for the amount of MPL. You state that this proposed specification is in line with the specifications applied to other GSK Bio vaccines. However, the results for this test have been reported as <3.00% (of the nominal value for the amount of MPL) for most, if not all, of the lots of HPV vaccine discussed in the BLA. Please justify the chosen upper limit for this specification (b)(4) given that all results to date have been less than 3%.

The following comments refer to the manufacturing process for MPL (b)(4) described in Module 3.2.A.3 Novel Excipients:

17. Please provide a more detailed description of the specific procedures and resulting supportive data utilized to assess the identity of the *Salmonella minnesota* R595 Master Seed and Working Seed by the microbial identification system (MIS) p. 42.
18. Validation of the (b)(4) assay, which is used for quality control of the (b)(4) of the Master Seed and Working Seed, verified that standard USP indicator organisms and facility environmental isolates could be recovered and detected in (b)(4) samples (p. 47). Please provide a summary of this validation study and include a listing of the indicator organisms utilized to verify recovery and detection in the assay.
19. Regarding the validation of the inactivation of *Salmonella minnesota* R595 cells by (b)(4) (b)(4) during the (b)(4) process, (Figure 60; p. 115), you extrapolated (b)(4) of *S. Minnesota* R595 by (b)(4) far outside measured data (which consisted of only two experimental points). Please provide a more detailed description of the (b)(4) process and include supportive data utilized to assess the effectiveness of the (b)(4) process.
20. It is stated (p. 41) that any new Working Seed will have to comply with the QC tests presented in Table 4 and with the acceptance criteria of the full scale production process evaluation presented in Table 5, and that when a new Working Seed complies with these tests, you will notify the FDA of the results through annual reports submitted to MF (b)(4) for MPL. We request instead that the information be submitted as a Prior Approval Supplement to the BLA rather than as annual reports to MF (b)(4). Alternatively, you may submit this information (i.e., your plans for testing and the acceptance criteria for the new seed as well as your plans for the submitting the results) to the BLA as a comparability protocol for new *S. Minnesota* R595 Working Seeds.

## ASSAYS

21. Please submit details on how new reference standards for the type-specific serological assays will be characterized and qualified for use.
22. CBER notes that you propose (b)(4) limit for the assay range for the measurement of antibody in human serum samples. For example, in Module 5.3.5.4 (p. 7 of 52), VALDOC: HPV16EIA2PCV01, you state that there is (b)(4) limit to the analytical range of the assay. According to the ICH definition of the range, suitable level of precision, accuracy, and linearity should be demonstrated within the range. Please use this criterion to establish appropriate upper limits for the ranges of the assays.
23. We note a high level of operator variability, (b)(4), for all serological assay validations submitted (VALDOC:HPV31EIA; Tables 14 and 15, p. 27 of 53). Operator variability is the largest component and exceeds (b)(4). Please comment.
24. We note that there are several samples that demonstrated unusually high variability (VALDOC: HPV18EIA2PCV01; p. 18 of 52). For example, CV% for day+operator for sample 4 is above (b)(4) and CV% for day+operator+reagents is exceeding (b)(4) for 6 samples out of 16 reaching almost (b)(4) for sample 2. Please comment.

Review and comment on the proposed final labeling will be completed when the application is otherwise acceptable. Extensive revision of the proposed final labeling may be required based on any additional information relating to the safety and effectiveness of this drug product.

The Pediatric Research Equity Act (PREA) requires that all NDAs, BLAs, or supplemental applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment unless a waiver or deferral has been obtained. You have submitted a proposal to defer studies in males < 18 years of age and partially waive studies in females < 9 years of age. This proposal will be formally reviewed by FDA's Pediatric Review Committee prior to final action on the application.

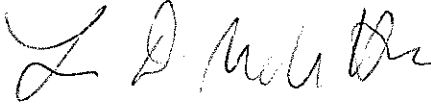
You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products February, 2000 (<http://www.fda.gov/cber/gdlns/mtpdufa.pdf>). For details, please also follow the instructions described in CBER's SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants (<http://www.fda.gov/cber/regsopp/81011.htm>).

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

If you have any questions, please contact the Regulatory Project Manager, Helen S. Gemignani, at (301) 827-3070.

Sincerely yours,

A handwritten signature in black ink, appearing to read "L D McVittie".

Loris D. McVittie, Ph.D.

Acting Director,

Division of Vaccines and Related Products Applications

Office of Vaccines Research and Review

Center for Biologics Evaluation and Research