Date: July 14, 2011

From: Nancy B. Miller, M.D.
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Subject: Clinical Review of Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant, Biologics License Application Efficacy Supplement

To: BLA STN 125259/132

Through: Lewis K. Schrager, M.D.
Chief, Clinical Review Branch 2
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Office of Vaccines Research and Review
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Food and Drug Administration

cc: Helen Gemignani

1 **Title and General Information**

1.1 Medical Officer's (M.O.) Review Identifiers and Dates

1.1.1 BLA #: STN 125259/132

1.1.2 Related IND #: (b)(4)

1.1.3 Reviewer's Name, Division and Mail Code (HFM number): Nancy B. Miller, M.D, DVRPA, HFM-475

1.1.4 Submission Received by FDA: September 21, 2010

1.1.5 Review Completed: July 14, 2011

1.2 Product

1.2.1 Proper Name: Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant

1.2.2 Trade Name: Cervarix

1.2.3 Product Formulation: Each 0.5 mL dose contains 20 µg HPV type 16 L1 protein, 20 µg HPV type 18 L1 protein, 50µg 3-O-desacyl-4'-monophosphoryl lipid A (MPL), and 0.5 mg of aluminum hydroxide. Each dose also contains 4.4 mg sodium chloride and 0.624 mg sodium dihydrogen phosphate dehydrate. Each dose may also contain residual amounts of insect cell and viral protein (<40 ng) and bacterial cell protein (<150 ng).

1.3 Applicant: GlaxoSmithKline

1.4 Pharmacologic Class or Category: Vaccine

1.5 Indication: No change in indications, which include prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18: cervical cancer, cervical intraepithelial neoplasia (CIN) grades 2 and 3 and adenocarcinoma in situ, and cervical intraepithelial neoplasia (CIN) grade 1

1.6 Proposed Populations: Extend population from 10-25 year old females to as young as 9 year old females.

1.7 Dosage Forms and Route of Administration: 0.5 mL suspension for injection as a single dose vial or pre-filled syringe. Three doses (0.5 mL each) are administered by intramuscular injection at 0, 1, and 6 months.

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3 **Executive Summary:** In the United States, recommendations from the Advisory Committee on Immunization of the Centers for Disease Control, indicate that females as young as 9 years of age may receive human papillomavirus (HPV) vaccination at the discretion of their physician.[1] With this supplement, the applicant is seeking approval to include females as young as 9 years old in the indicated age population.

When Cervarix was licensed on October 16, 2009, safety data was available for females 10-25 years of age. The approval letter advised GlaxoSmithKline (GSK) of the requirement to perform a pediatric post-marketing study including 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 post-marketing study by June 30, 2010. The clinical study noted in the approval letter was entitled: "A clinical study to evaluate safety and immunogenicity of GSK's HPV bivalent (Types 16 and 18) vaccine, recombinant when administered to healthy females 9 through 25 years of age." The approval letter also stated that FDA waived 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 (i.e., HPV-16 and HPV-18 related cervical cancer and cervical dysplasias).

Study HPV-048 is a Phase I/II, partially blind, randomized, multicenter, age-stratified, dose-range study in healthy females 9-25 years of age to assess safety and immunogenicity of two formulations of GSK Biologicals' HPV 16/18 vaccine [20µg HPV 16 VLP/20µg HPV 18 VLP adjuvanted with 50µg 3-O-desacyl-4'-monophosphoryl lipid A (MPL), and 0.5 mg of aluminum hydroxide (AS04) or 40µg HPV 16 VLP/40µg HPV 18 VLP adjuvanted with AS04] administered intramuscularly according to a 2-dose schedule (0, 2 months or 0, 6 months) when compared to the standard 3-dose schedule (0, 1, and 6 months) of the licensed formulation of Cervarix [20µg HPV 16 VLP/20µg HPV 18 VLP adjuvanted with AS04]. There were four arms in this study: Group 1 received 20µg/20µg HPV 16/18-AS04 at 0, 1, and 6 months; Group 2 received 20µg/20µg HPV 16/18-AS04 at 0 and 6 months; Group 3 received 40µg/40µg HPV 16/18-AS04 at 0 and 6 months; and Group 4 received 20µg/20µg HPV 16/18-AS04 at 0 and 2 months. Safety was reviewed for all treatment groups, with focus on subjects who received any dose of the licensed formulation. The results of this study support inclusion of females as young as 9 years of age in the indicated population.

Clinical and Regulatory Background: HPV serotypes 16 and 18, included in Cervarix, are the most common HPV serotypes associated with the development of cervical intraepithelial neoplasia (CIN) and cervical cancer. These HPV serotypes are transmitted through sexual activity. The 2009 Youth Behavioral Risk Survey indicated that 46.0% of high school students had ever had engaged in sexual intercourse (46.1% male and 45.7% female). In that same survey, the percentage of subjects who were sexually active before

[1] http://www.cdc.gov/vaccines/recs/schedules/default.htm (Adolescent schedule 7-18 years)

age 13 years was reported to be 5.9%.[2], which represented an increase from the 2005 Survey rate of 3.7%.[3] Further, analyses of vaccine efficacy in the pivotal efficacy studies for both Gardasil (quadrivalent HPV 6, 11, 16, 18 VLP vaccine adjuvanted with aluminum) and Cervarix have demonstrated that the vaccines are prophylactic and are of greatest benefit when administered to subjects who have not been exposed to the vaccine HPV types prior to vaccination.

Efficacy Assessment in females 9 through 14 years of age: The efficacy assessment supporting the initial licensure of Cervarix in females 10-25 years of age (October, 2009) was made by bridging the immune responses from15-25 year old females, in whom clinical efficacy was assessed by demonstration of significant decrease in advanced cervical dysplasia related to vaccine HPV types 16 and/or 18, [i.e., Cervical Intraepithelial Neoplasia or CIN Grade 2 or worse and Adenocarcinoma in Situ or AIS], to females 10-14 years of age, in whom genital exams were not feasible but who were expected to derive highest benefit from the vaccine. The supplemental report for study HPV-048 provided post-hoc bridging immunogenicity analyses requested by CBER to demonstrate that Cervarix, when administered to females 9-14 years of age, elicits a non-inferior immune response when compared to females 15-25 years of age, the age group in which efficacy of the vaccine was originally assessed. Pre-defined immunogenicity non-inferiority margins were met. CBER considered the demonstration of non-inferiority of immune responses to HPV-16 and HPV-18 at 1 month after dose 3 Cervarix to support demonstration of efficacy in females as young as 9 years of age.

Safety Assessment in Females 9 through 25 years of age: Safety data was reviewed from study HPV-048 in pediatric females 9 through 17 years of age and in adult females 18 through 25 years of age who received at least one dose of the licensed formulation of Cervarix. Further comparisons were made to the safety data from the larger studies in both age groups which supported the original approval of Cervarix in 2009. In addition, safety was assessed in subjects in those age strata who received the higher-dose formulation in order to rule out unexpected safety signals in all ages, but with focus on the pediatric subjects. With study HPV-048, additional safety data was provided in 253 subjects 9-17 years of age who received any dose of the licensed formulation of Cervarix. An additional 257 subjects 9-17 years of age received any dose of the higher dose formulation of HPV 16/18 vaccine. Assessing the total pediatric age exposure in clinical studies to date in which the licensed formulation was administered according to 0, 1 and 6 month schedule, the total number of subjects 9-14 years of age was increased to1275 females (additional 82 subjects in Group 1), and the total number of subjects 15-17 years was increased to 6362 (additional 46 subjects in Group 1), with an overall exposure in the pediatric age range of 7367 in females 9-17 years of age.

[2] CDC. Youth Risk Behavioral Surveillance. United States – 2009. MMWR 2010; 59(SS-5): 1-142.
[3] CDC. Youth Risk Behavioral Surveillance. United States – 2005. MMWR 2006; 55(SS-5): 1-112.

Safety was reviewed by age groups from the datasets provided. Proportions of subjects with solicited local and general adverse events days 0-6 after vaccination, unsolicited adverse events in the 30 days after vaccination, and serious adverse events were similar in the two age strata (9-17 years and 18-25 years), and also were comparable to findings reported in the original Cervarix package insert (9-14 in HPV-048 compared to original studies in 10-14 years and 15-25 years in HPV-048 compared to original studies in subjects 15-25 years of age). In study HPV-048, no serious adverse events were noted in subjects who were 9 years of age at the time of vaccination in any of the treatment groups.

CBER further considered the worldwide experience with Cervarix in females as young as 9 years in assessment of safety in consideration of revising the indicated age population. In review of the data provided from the Post-Marketing Safety Update Report in subjects 9 through 17 years of age through 11/17/10 (with ---(b)(4)--- doses distributed), the most frequently reported adverse events (MedDRA preferred terms) were headache, injection site pain, pyrexia, nausea and dizziness, which were similar to the rates and occurrence in all age groups. Most of the reporting rates for the 9 through 17 year old population were lower than that noted for the overall age group.

In summary, given the large number of pediatric subjects 9-17 years of age whose safety was assessed in studies in which the licensed formulation of Cervarix was administered at the licensed dosing schedule (N= 7367), the safety findings for subjects as young as 9 years of age who received the licensed formulation in study HPV-048, the safety findings as compared to those in the larger studies which supported initial licensure of Cervarix in subjects as young as 10-25 years of age, the developmental similarities between subjects 9 and 10 years of age, the worldwide experience with Cervarix in children as young as 9 years of age, and the precedent with licensure of other pediatric vaccines, the pooled safety data supported the applicant's request to extend the lower age indication to 9 years of age. CBER is requesting that the age of inclusion of post-marketing safety assessments be extended to females as young as 9 years of age in the established post-marketing observational safety study underway in large managed care organizations in the US.

4 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC): No additional data were provided with this supplemental BLA.

4.2 Animal Pharmacology/Toxicology: No additional data were submitted with this supplemental BLA.

5 Clinical and Regulatory Background

5.1 Disease or Health-Related Condition(s) Studied and Available Interventions: More than 100 types of HPV exist, and more than 40 of these can infect the

genital area.[4] Genital HPV infection is the most common sexually transmitted infection in the United States (Centers for Disease Control and Prevention (CDC) estimates that more than 6 million people are infected each year.)[5] Most of these infections are self-limited, although certain high-risk HPV types are known to be carcinogenic. HPV-16 (alpha-9) and HPV-18 (alpha-7) were classified as cervical carcinogens by the World Health Organization International Agency for Research and Cancer in 1995, and HPV-31 and HPV-33 (alpha-9) were categorized as probably carcinogenic.[6,7] HPV-16 is considered a very efficient carcinogen, and is associated with approximately 55% of cervical cancers globally. HPV-18 is another important oncogenic HPV type and is associated with adenocarcinoma and another approximately 16% of other cervical cancers. In 2010 in the United States, the American Cancer Society estimated that approximately 12,200 new cases of invasive cervical cancer would be diagnosed and approximately 4,210 women would die from cervical cancer. Treatment of HPV infection involves removal of lesions that result from HPV infection. The two available preventive vaccines, Cervarix (GSK) and Gardasil (Merck), are most effective when administered prior to onset of sexual activity, and therefore, prior to exposure to vaccine HPV related types. ACIP has included subjects as young as 9 years of age in their recommendations for vaccination. Subjects as young as 9-years of age are included in the present application to make the vaccine available to subjects of this age group and provide Cervarix as an option for administration in vaccination programs. The duration of effectiveness is estimated to be between five to six years or more for Gardasil and Cervarix (to date), although there is evidence that the monovalent HPV-16 vaccine used in product development of Gardasil provides protection out to 8.5 years in subjects who were naïve for HPV-16 at time of vaccination and received three doses of the monovalent HPV-16 vaccine according to protocol.[8]

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products: Cervarix is one of two vaccines approved for use in the U.S. to prevent cervical pre-cancers and cancers associated with high-risk HPV types -16 and -18. Cervarix is approved for use in females 10-25 years of age for this indication. Gardasil is a quadrivalent HPV 6, 11, 16, 18 VLP vaccine (adjuvanted with aluminum) which is indicated for prevention of cervical precancers and cancers and vulvar and vaginal precancers and cancers. Further, Gardasil is indicated for prevention of vaccine HPV-anal precancers and cancers

[4] Centers for Disease Prevention and Control. Sexually transmitted diseases treatment guidelines – 2010. MMWR Recomm Rep 2010; 59 (RR-12): 1-110.
[5] CDC. Quadrivalent Human Papillomavirus Vaccine, Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007; 56 (RR02):1-24.
[6] Schiffman M et al. Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. Infectious Agents and Cancer 2009; 4:8
[7] Schiffman M et al. Human papillomavirus and cervical cancer, The Lancet 2007; 370 (9590): 890-907
[8] Rowhani-Rahbar A et al. Longer term efficacy of a prophylactic monovalent HPV type 16 vaccine. Vaccine 2009; 27(41): 5612-9.

in females and males 9-26 years of age, as well as prevention of genital warts in related to HPV types 6 and 11 in females and males 9-26 years of age.

5.3 Previous Human Experience with the Product Including Foreign Experience: Cervarix was licensed for use in Australia in May, 2007 and received marketing approval by the European Medical EA September 24, 2007 prior to licensure in the United States on 10/16/2009. Cervarix is licensed for use in more than 100 countries worldwide. (www.ema.europa.eu). The vaccine has been used worldwide for more than three years with an estimated ---(b)(4)--- doses distributed as of 11/17/10. The marketing authorization for Cervarix was amended by the European Commission in August 2010 to extend the indication of Cervarix to include prevention of cervical precancers and cancers to include HPV types 31, 33, and 45. The EPAR –Assesssment Report – Variation is located at the following website (go to Assessment History tab). http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000721/human_med_000694.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125

5.4 Regulatory Background Information: Table 1 contains a regulatory timeline for review of this supplement.

Table 1: Regulatory Timeline for STN 125259/132 [CBER generated]

Date	Action
10/16/09	Cervarix approved in U.S.
6/17/10	Submission of clinical study report for HPV-048 to satisfy submission of post-marketing requirement before 6/30/10. Included post-hoc analysis for bridging immune responses from females 15-25 years to subjects 9-14 years of age. Datasets not available at this time.
9/20/10	Submission of supplement 125259/132.0 with draft labeling to extend indication to females as young as 9 years of age.
9/22/10	Submission of datasets for study HPV-048 (prepared by a blinded statistician) [STN 125259/132.1]
10/14/10	As requested on 10/7/10, clinical study report for HPV-048 re-submitted to STN 125259/132.2].
11/8/10	Request for Pharmacovigilance Plan (PVP) by reviewer from Office of Biostatistics and Epidemiology (OBE)
11/22/10	IR sent for additional Serious Adverse Event (SAE) narratives.
12/7/10	As requested on 11/22/10, GSK submitted the complete set of Council for International Organizations of Medical Sciences (CIOMS) adverse event reports for all serious adverse events included in the clinical study report and datasets [STN 125259/132.3].
12/14/10	Information response (IR) request for most recent Post-marketing Safety Update Report (PSUR) by OBE
1/4/11	IR request for subject 1546 (contraceptive use)
1/20/11	First labeling meeting. Comments/requests sent to GSK after this meeting.
1/25/11	IR sent to GSK on subjects identified from reaccod.xpt dataset (urticaria)
1/31/11	GSK submits requested PVP plan and PSUR 2009-2010
1/31/11	IR comments sent to GSK re: total pediatric subjects, doses distributed [with focus on 9 year olds if available], outcome of 3 ongoing pregnancies, and 2 statistical questions.
2/1/11	Submission of PVP and PSURs. In addition, response regarding requests for update of package insert (PI) and explanation for not including subjects from study HPV-048 into adverse event tables with subjects from other studies [STN 125259/132.4]
2/9/11	Submission of additional information on subject 1546 re: OC use clarification [STN 125259/132.5]
2/11/10	Mid-cycle meeting
3/2/11	Partial responses to IRs sent 1/31/11 [STN 125259/132.6]
3/9/10	Pediatric Equity Research Committee (PERC) Presentation
4/8/11	Partial response to requests for information on subjects 9 through 17 years of age from post-marketing experience. [STN 125259.132.7]
4/11/11	Additional comments on PI sent by email to GSK.
6/6/11	Responses to IR sent 1/25/11. [STN 125259.132.8]
6/14/11	PI returned with revisions as requested on 4/11/11. [STN 125259/132.9]
7/14/11	Revised PI sent to GSK via email.
7/22/11	Approval of age indication to females as young as 9 years of age.

6 Clinical Data Sources (both IND and non-IND), Review Strategy and Data Integrity

6.1 Material Reviewed

6.1.1 BLA Number Which Serves as a Basis for the Clinical Review:

BLA 125259/132 served as the basis for the clinical review. GSK had submitted the study report to STN 125259/106, and CBER requested that this study report be submitted in entirety to STN 125259/132 to have all study-related documents in the present supplement.

6.1.2 Literature:

References are included in footnotes to this document.

6.1.3 Post-Marketing Experience: Dr. Michael Nguyen of the Office of Biostatistics and Epidemiology (OBE) requested a Post-marketing Pharmacovigilance plan (PVP). This was submitted in STN 125259/132.4 dated December 2010 (see separate bioepidemiology review for comments). As noted by Dr. Michael Ngyuen in his separate bioepidemiology review, use of Cervarix in the United States has been limited. Cervarix has been used more extensively in the United Kingdom as part of their in-school vaccination program with more than ---(b)(4)-- doses distributed to date, and the British Medical and Health Care Products Regulatory Agency has concluded that the vaccine's safety profile is consistent with clinical trial data and no new safety issues were identified.

6.2 Table of Clinical Studies: See Table 2.

Table 2: Clinical Studies [CBER generated]

Study Number	Group # - HPV 16µg/18µg formulation @ time of administration	Phase	Endpoint	Total Sample Size	Geographic Distribution of Study Population	Dates Conducted
Study HPV-048	Group 1 - 20µg/20µg @ 0,1, 6 months Group 2 - 20µg/20µg @ 0,6 months Group 3 – 40µg /40µg @ 0,6 months Group 4 – 40 µg /40µg @ 0,2 months	I/II	Primary Immunogenicity: HPV 16/18 antibody titers (by ELISA) assessed one month after the last dose of vaccine when administered at different dosages (20µg or 40µg of each HPV type) and on different schedules (0, 2; 0, 6; and 0, 1, 6 months). Primary safety: Solicited local and general adverse events within 7 days of vaccination.	See Table 1	21 centers in Germany and Canada	10/17/07-10/23/08 for primary analysis; ongoing through Month 24 for all subjects to collect follow-up immunogenicity and safety. [M7 completion-10/20/08; M12 completion-4/20/09; M18 complete-10/23/09]

6.3 Review Strategy: The Clinical study report for study HPV-048 was reviewed by this clinical reviewer. Immunogenicity analyses were reviewed by the CBER biostatistician. In addition, safety was assessed in females 9 through 17 years of age and in females 18 through 25 years of age, as well as in females 9 through 14 years of age and females 15 through 25 years of age to observationally compare rates of adverse events in study HPV-048 and the studies which supported initial licensure of Cervarix (safety data in package insert). CBER primarily considered safety findings in Groups 1 and 2 in which subjects received the licensed formulation of Cervarix, but adverse events were also considered in Groups 3 and 4 to further assess safety in the pediatric population.

6.4 Good Clinical Practices (GCP) and Data Integrity: Study HPV-048 was a non-IND study conducted in 21 centers in Canada and Germany. The list of investigators was reviewed in collaboration with the Bioresearch Monitoring

Branch (BIMO). Because of the relatively small study size, the multiplicity of sites, the relatively small number of pediatric subjects enrolled at each site, and it was not feasible to visit the multiple sites throughout Canada and Germany, after discussion with BIMO reviewer, Dennis Cato, it was decided that a separate BIMO inspection would not be conducted for this BLA supplement.

Reviewer's Comment: This approach was appropriate for this application as BIMO inspections were conducted for the original BLA for this product.

6.5 Financial Disclosures: The documents provided by GSK indicate that one investigator, Dr. Tino Schwartz, received significant payments (including payments to spouse and dependent children, and payments to an affiliated institution directly supporting, or made on behalf of the investigator) of more than ----------(b)(4)---------- for honoraria). GSK notes that Dr. Schwartz enrolled 44 (4.58%) of the 961 subjects enrolled in the total study. An external statistician reportedly monitored enrollment, and enrollment by Dr. Schwartz was kept below 5% of the total recruitment to reduce the risk of bias. No other investigators were identified with disclosable financial interests/arrangements. CBER noted these financial disclosures and concluded that GSK's efforts to minimize potential bias due to financial conflicts of interest were adequate.

7 Immunogenicity: As noted in the original clinical review of Cervarix, because there were so few cases of breakthrough infections or vaccine HPV-type related dysplasias in subjects who were not yet exposed to these vaccine HPV types, an immune correlate of protection could not be identified. Up to 76 months following first vaccination in study HPV-001 (up to 70 months following completion of the full vaccination course), 98.6% or more of the vaccinees in the According to Protocol (ATP) population for Immunogenicity remained seropositive for both HPV-16 and HPV-18 IgG antibodies as measured by enzyme-linked immunosorbent assay (ELISA). Geometric mean titer (GMT) levels for both HPV-16 and HPV-18 reached a plateau during study HPV-007 at approximately one log below the peak response level observed at Month 7 (in study HPV-001) without evidence of apparent further decline between Month 18 and the last time intervals evaluated (Months 69-74 and 75-76). Seropositivity rates and GMTs were very similar in the Total Vaccinated Cohort as compared to the ATP cohort for immunogenicity out to Months 69-74 and Months 76-76. GMTs in the vaccine group were much higher than subjects in the control group and persisted through Month 76.

8 Clinical Studies

Indication #1: Lower age indication to include females 9 years of age.

8.1 Trial # 1: Clinical Study Report for 110659 (HPV-048), "Evaluation of the safety and immunogenicity of GSK's 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" and Supplemental Report to study HPV-048.

Study start date: 10/17/07; **Data lock point:** 12/10/09; **Date of report:** 5/17/10

Total Study Duration Planned: 24 months for extended safety and immunogenicity

Study Sites: 21 centers in Canada and Germany.

Objectives: See Appendix 1

Reviewer's Comment: The results of certain primary and secondary objectives were not considered pertinent to inclusion of females as young as 9 years of age for study HPV-048, and are located in Appendix 1. The high-dose formulation is not approved for use in the US, nor are alternative dosing regimens. Although safety assessments for all subjects were considered within the review, the focus of the safety review centered on those subjects who received any dose of the licensed formulation. The post-hoc immunogenicity analysis involved comparison of immune responses to HPV-16 and HPV-18 by GMT ratio in the ATP cohort for immunogenicity in Group 1. This analysis was the focus of the immunogenicity assessment. Demonstration of non-inferiority of immune responses to HPV-16 and HPV-18 provides support for inferring efficacy in females as young as 9 years of age. This post-hoc analysis is similar to analyses conducted for subjects 10-14 years of age and 15-25 years of age at the time of original approval. The results of other pre-specified objectives regarding comparison of immunogenicity and safety results for the different formulations and regimens and results were included in Appendix 1, since they did not impact on decisions relating to this supplemental BLA, nor will they support change in dosing regimen or formulation in the US.

Co-Primary Objectives:

- **Immunogenicity** – See Appendix 1.
- **Safety** – Evaluate the reactogenicity of the HPV 16/18 L1 VLP AS04 vaccine when administered at different dosages (20 or 40µg of each HPV type) and on different schedules (0, 2 or 0, 6 months) with respect to the occurrence, intensity and relationship to vaccination of solicited local and general symptoms reported within 7 days (Days 0-6) after each and any vaccination. [Safety discussed within this review.]

Secondary Objectives:

- **Immunogenicity** – See Appendix 1.
- **Safety – [**Safety discussed within this review].
  - Evaluate safety of the vaccine when administered at different doses and different schedules to Month 7.
  - Evaluate safety of the vaccine when administered at different doses and different schedule from Month 7 through Month 24.

Reviewer's Comment: Safety was reviewed for subjects in Group 1 and Group 2 who received the licensed formulation of Cervarix (20µg HPV-16/20 µg HPV-18) according to the standard dosing regimen (Months 0, 1 and 6) or at an alternate dosing schedule (i.e., Months 0 and 6), as well as in subjects who received the higher-dose formulation of HPV 16/18 – AS04 vaccine at Months 0 and 6 or Months 0 and 2.

Design Overview: Phase I/II, partially blind, controlled, randomized, age-stratified trial with four parallel groups. Each group was stratified into three age strata: 9-14, 15-19, and 20-25 years of age. The numbers of subjects planned in each group are shown in Table 3.

Table 3: Study HPV-048 - Study Design Summary (Planned)

Group*	HPV 16/18 dosages (μg/ μg)	Schedule	Age strata (years)	N
40/40 M 0, 2	40/40	0, 2 months	9-14 15-19 20-25	80 80 80
40/40 M 0, 6	40/40	0, 6 months	9-14 15-19 20-25	80 80 80
20/20 M 0, 6	20/20	0, 6 months	9-14 15-19 20-25	80 80 80
Cervarix M0, 1, 6	20/20	0, 1, 6 months	9-14 15-19 20-25	80 80 80
TOTAL				960

*For blinding within these groups, an aluminum hydroxide control was administered at Month 6 (Group 40/40 M0, 2) or at Month 2 (Groups 40/40 M0, 6 and 20/20 M0, 6). The Cervarix group 0, 1, 6 was not blinded.
Source: STN 125259/132.2, Study HPV-048, Module 5.3.5.1.3, p. 43

Study Visits: There were seven visits for the 3-dose group (including blood samples drawn at Month 0, Month 7, Month 12, Month 18, and Month 24). There were eight visits for subjects in the 2-dose Group (including blood samples drawn at Month 0, Month 3, Month 7, Month 12, Month 18, and Month 24).

Planned Population: Nine hundred and sixty subjects (240 subjects in each group, 80 subjects per age stratum) were planned to be enrolled to provide 768 subjects evaluable for the immunogenicity of the vaccine one month after the last dose. Inclusion criteria were as follows: healthy females 9-25 years of age, with written informed consent/assent depending on age of subject, of non-childbearing potential or using appropriate contraception. Exclusion criteria: received investigational product within 30 days of first dose of study vaccine, chronic administration of steroids or immuosuppressants, participating in another clinical study, planned administration of another vaccine not foreseen by study (acceptable vaccines and time frames specified in protocol), pregnant or breastfeeding, planning to become pregnant up to 2 months of last study dose, previous vaccination with HPV vaccine, previous administration of MPL or AS04 adjuvant, cancer or autoimmune disease under treatment, immunodeficiency, history of allergic disease likely to be exacerbated by components of vaccine or latex; acute disease at time of enrollment (could be deferred until improved), clinically significant acute or chronic disease, administration of immunoglobulins or blood products within three months preceding dose.

Products mandated by the protocol: See Table 4.

Table 4: Study HPV-048- Study vaccines and placebo

Group	Vaccine/placebo	Formulation	Lot Number	Presentation	Volume	# of doses
40 µg HPV-16/ 40 µg HPV-18 (M0, 2) And 40 µg HPV-16/ 40 µg HPV-18 (M0, 6)	HPV 16/18 L1 VLP 40µg/40µg AS04	40µg HPV 16 L1 protein 40µg HPV 18 L1 protein 50µg 3-O-desacyl-4'-monophosphoryl lipid A (MPL) 500µg aluminum hydroxide $[Al(OH)_3]$	DHPVA025A	Liquid in pre-filled syringes	0.5mL	2
	Placebo	500µg $[Al(OH)_3]$ 150mM NaCl 8mM $NaH_2PO_4.2H_2O$ q.s. ad 0.5mL water for injection	PHPVA009A	Glass vials	0.5mL	1
20 µg HPV-16/ 20µg HPV-18 (M0, 6)	HPV 16/18 L1 VLP 20µg/20µg AS04	20µg HPV 16 L1 protein 20µg HPV 18 L1 protein 50µg 3-O-desacyl-4'-monophosphoryl lipid A (MPL) 500µg aluminum hydroxide $[Al(OH)_3]$	AHPVA006A	Glass vials	0.5mL	2
	Placebo	500µg $[Al(OH)_3]$ 150mM NaCl 8mM $NaH_2PO_4.2H_2O$ q.s. ad 0.5mL water for injection	PHPVA009A	Glass vials	0.5mL	1
20 µg HPV-16/ 20 µg HPV-18 (M0, 1, 6)	HPV 16/18 L1 VLP 20µg/20µg AS04	20µg HPV 16 L1 protein 20µg HPV 18 L1 protein 50µg 3-O-desacyl-4'-monophosphoryl lipid A (MPL) 500µg aluminum hydroxide $[Al(OH)_3]$	AHPVA006A	Glass vials	0.5mL	3

Source: STN 125259/132.2, Module 5.3.5.1.4, CSR HPV-048, Table 5, p. 54

Dosage and Administration: Subjects received either the licensed formulation of Cervarix (i.e., contained 20µg HPV-16 nd 20µg HPV-18 with AS04) or received a higher than usual formulation (i.e., contained 40µg HPV-16 and 40µg HPV-18 with AS04). Dosing varied:

- **0, 2 month schedule** - subjects received HPV vaccine at Months 0 and 2, and aluminum hydroxide placebo at Month 6.
- **0, 6 month schedule** – subjects received HPV vaccine at Months 0 and 6, and aluminum hydroxide placebo at Month 2.
- **0, 1, 6 month schedule** – subjects received HPV vaccine at Months 0, 1, and 6. All vaccinations were administered intramuscularly into the non-dominant deltoid muscle.

Laboratory Assays: Quantitative anti-HPV 16 and anti-HPV-18 antibodies were measured by Enzyme-Linked Immunosorbent Assay (ELISA), with cut-off of 8 EL.U/mL for anti-HPV-16 and 7 EL.U/mL for anti-HPV 18 (run by GSK Biologicals or validated laboratory designated by GSK). Laboratory tests run by the local labs included

chemistries (alanine aminotransferase and creatinine) and hematology labs (white blood cells and differential, red blood cells, platelets and hematocrit.

Safety Endpoints

Adverse Events: Assessment of adverse events in study HPV-048 was generally similar to assessment of safety in studies which supported original licensure of Cervarix. Therefore, observational comparisons, although post-hoc in nature, were considered supportive of approval of use of Cervarix in females as young as 9 years of age.

- **All adverse events (AEs)** occurring within 30 days following administration of each dose of vaccine
- **Serious adverse events (SAEs)** were collected from time of first dose of vaccine to end of study (up to Month 24).
- **Medically significant adverse events (MSAEs),** i.e., prompting emergency room visits or not related to common conditions and resulting in physician visits, occurring throughout the study period (up to Month 24)
- **Solicited AEs** occurring within 7 days (days 0-6) after each vaccination were to be recorded on a diary card. Urticaria/rash within 30 minutes of vaccine administration was documented by investigator.
- **Solicited local AEs** included: pain at injection site, redness at injection site, and swelling at injection site.
- **Solicited general AEs** included fever, headache, fatigue, gastrointestinal symptoms (nausea, vomiting, diarrhea, and/or abdominal pain), arthralgia, myalgia, rash, and urticaria.

Grading of Adverse Events

Solicited AEs were graded as follows**:**

- **Pain** – grade 0 (absent), grade 1 (painful on touch), grade 2 (painful when moved), grade 3 (pain that prevented movement.
- **Redness and swelling at injection site** were measured as the greatest surface diameter in mm and graded as follows: grade 0 (none), grade 1 (>0 mm to ≤20 mm), grade 2 (>20 mm to ≤50 mm), and grade 3 (>50 mm).
- **Fever** was recorded in ˚C and was defined as oral/axillary temperature ≥ 37.5˚C and graded as follows: grade 0 (≤ 37.5 ˚C), grade 1 (≥37.5°C (99.5°F) to ≤38.0°C (100.4°F), grade 2 (>38.0°C (100.4°F) to ≤39.0°C (102.2°F), and grade 3 (>39.0°C (102.2°F).
- **Headache, fatigue, Gastrointestinal symptoms, arthralgia** (only in joints distal from injection site), **myalgia, and rash** were graded similar to pain: grade 0 (absent), grade 1 (easily tolerated), grade 2 (interfered with normal activity), and grade 3 (prevented normal activity).
- **Urticaria** was graded as follows: grade 0 (normal), grade 1 (urticaria on a single body area), grade 2 (urticaria on 2 or 3 body areas but not more), and grade 3 (urticaria on at least 4 body areas).

Unsolicited AEs were graded as mild or grade 1(easily tolerated), moderate or grade 2 (interferes with normal activities), and severe or grade 3 (prevents normal activity).

Causality were assessed by the investigator.

Pregnancy information was to be collected on any subjects who became pregnant while participating in the study. Pregnancy outcomes were reported.

Statistical considerations: The original sample size for study HPV-048 was based on the primary and secondary immunogenicity analyses. Please see Appendix 1.

Post-hoc immunogenicity analyses: CBER's assessment of immunogenicity data involved post-hoc analyses to demonstrate non-inferiority of immune responses to HPV-16 and HPV-18 at 1 month after dose 3 of the licensed formulation of Cervarix administered according to the licensed schedule elicited in subjects 9-14 years of age as compared to subjects 15-25 years of age. 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.

Cohorts planned for Analysis:

- The **Total Vaccinated Cohort** included all subjects who received at least one dose vaccine and for whom data for safety or immunogenicity were available.
- **According to Protocol (ATP) cohort for safety:** received all doses of vaccine/placebo for group assigned to each respective group, had at least one dose with safety data, had not received forbidden vaccine, and for whom the randomized code was not broken (for the three 2-dose groups).
- **ATP cohort for immunogenicity:** met all eligibility criteria, with immunogenicity data available.

Populations enrolled and analyzed: Safety was reviewed in all subjects in the Total Vaccinated Cohorts (TVC) for Groups 1 – 4. Immunogenicity was analyzed in subjects in Group 1 who were part of the ATP cohort.

Enrollment and withdrawal information for subjects enrolled in study HPV-048 are presented in Table 5.

Table 5: Study HPV-048 - Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total Vaccinated cohort)

	Group 1 20µg/20µg @ M0, 1, 6	Group 2 20µg/20µg @ M0, 6	Group 3(c) 40µg/40µg @M0, 6	Group 4(d) 40µg/40µg @ M0, 2
Number of subjects vaccinated	239	240	241	240
Number of subjects completed last study visit	234	229	238	213*
Number of subjects who withdrew from study	5 (a)	11(b)	13(c)	9*(d)
Reasons for withdrawal				
Serious Adverse Event	0	0	0	0
Non-Serious Adverse Event	0	0	0	0
Protocol violation	0	0	0	0
Consent withdrawal not due to AE	2	4	4	2
Moved from study area	0	1	1	0
Lost to follow-up (incomplete vaccination)	3	3	5	4
Lost to follow-up (complete vaccination)	0	2	2	0*
Others	0	1	1	3

(a) Group 1 - Subjects 293[21], 808[17] and 1543[16] were lost to follow-up, and 524[19] and 823[19] withdrew consent.
(b) Group 2 – Subjects 60[24] migrated from study area; 12[21], 203[13], 831[23], 259[21], and 277[20] were lost to follow-up; 232,[9] 531[14], 511[21], and 2219[20] withdrew consent; and 1921[19] became pregnant.
(c)Group 3-Subjects 519[16], 1578[11], 1591[14], and 1661[10] withdrew consent. Subjects 195[20], 264[23], 512[17], 807[19], 835[20], 1560[24], 2105[20], and 294[25] migrated from study area. Subject 1593[18] did not want additional vaccination.
(d) Group 4-Subjects 818[23] was non-compliant with study. Subject 1577[13] did not want additional blood drawn. Subjects 192[9] and 290[20] withdrew consent. Subjects 204[9], 287[11], 805[20], 2473[19] were lost to follow-up. Subjects 625 was considered withdrawn because she did not return for on last visit.
[#] = [age of subject]
Source: STN 125259/106, CSR HPV-048, Table 18, p. 82 and wdrop.xpt dataset

Reviewer's Comment: There were few relatively few withdrawals across the study, and proportions were generally balanced (all ≤ 5.4%). None were related to the occurrence of a serious adverse event or a non-serious adverse event.

Demographics of Groups 1 and 2 for ages 9-14 years and 15-25 years of age: The mean age in Group 1 was 17.2 years and in Group 2 was 17.3 years. The vast majority of subjects in each group were of white/Caucasian ethnic background (233/239 or 97.5% in Group 1 and 229/240 or 95.4% in Group 2). Other ethnic groups included African and African American, American Indian, Asian or "others". Similar demographics were noted in groups 3 and 4.

Breakdown of all groups by age strata (9-14 years, 15-19 years, and 20-25 years) is presented in Table 6, and breakdown of Groups 1, 2, 3 and 4 by age is presented in Table 7. The numbers in each of the strata in Table 8 were calculated to provide totals in the pediatric age group for all subjects (9-17 years and adult subjects (18-25 years) as well as the age strata used in calculations to compare immune response (9-14 years and 15-25 years).

Table 6: Study HPV-048 - Demography: age (in years) at vaccination dose for each group, by age strata (Total Vaccinated cohort) [Groups 1 and 2]

Group	Subgroup	N	n	Mean	SD
Group 1: 20 µg HPV-16/ 20 µg HPV-18 @M0, 1, 6	9-14	82	82	12.4	1.71
	15-19	76	76	17.0	1.48
	20-25	81	81	22.3	1.63
Group 2: 20 µg HPV-16/ 20 µg HPV-18 @M0, 6	9-14	78	78	12.6	1.56
	15-19	82	82	17.0	1.47
	20-25	80	80	22.3	1.75
Group 3: 40 µg HPV-16/ 40 µg HPV-18 @M0, 6	9-14	77	77	12.3	1.64
	15-19	84	84	16.9	1.47
	20-25	80	80	22.1	1.71
Group 4: 40 µg HPV-16/ 40 µg HPV-18 @M0, 2	9-14	82	82	12.3	1.63
	15-19	80	80	17.1	1.44
	20-25	78	78	22.1	1.69

9-14 = 9 through 14 years; 15-19 = 15 through 19 years
20-25 = 20 through 25 years
N = number of subjects with documentation on age and gender
n = number of subjects with age value
SD = standard deviation
Source: STN 125259/106, CSR HPV-048, Table 20, p.84

Table 7: Study HPV-048 – Demography: age (in years) at vaccination dose for each group by age (Total Vaccinated Cohort) [Groups 1, 2, 3, 4]

Ages years	Group 1 20 µg HPV-16/20 µg HPV-18 @M0, 1, 6	Group 2 20 µg HPV-16/20 µg HPV-18 @M0, 6	Group 3 20 µg HPV-16/20 µg HPV-18 @M0, 6	Group 4 20 µg HPV-16/20 µg HPV-18 @M0, 2
TOTAL 9-14 years	82	78	77	82
TOTAL 15-25 years	157	162	164	158
TOTAL 9-17 years	128	125	128	130
TOTAL 18-25 years	111	115	113	111

Number of subjects in age groups from STN 125259/132.1, Module 5.3.5.25.3.1 WDEMOG.xpt dataset

Reviewer's Comment: While small, the numbers of subjects was considered robust enough to permit adequate consideration of immunogenicity in subjects 9-14 years of age as compared to subjects 15-25 years of age.

IMMUNOGENCITY RESULTS

Using immunogenicity results from study HPV-048 to support bridging immune response from females 15-25 years of age with females 9-14 years of age (Group 1 subjects): A post-hoc analysis was performed to assess non-inferiority (NI) of the immune response after dose 3 Cervarix (administered at 0, 1, and 6 months) in 9-14 year old subjects versus 15-25 year old subjects who received Cervarix 20µg/20 µg at 0, 1, and 6 months.

Criterion for NI: NI of the immune response would be demonstrated if the lower limit of the 95% Confidence Interval (CI) of the Geometric Mean Titer (GMT) ratio of 9-14 year old females over the 15-25 year old females was above the pre-defined limit of 0.5. This analysis was conducted in both the ATP cohort and the TVC cohort, and NI was demonstrated in both cohorts. Please see Table 8 (ATP cohort) and Table 9 (TVC cohort) for comparisons for the 9-14 year age stratum and the 15-25 year age stratum.

Table 8: Study HPV-048 – Non-inferiority of the anti-HPV 16 and anti-HPV 18 response to Cervarix in 9-14 year old females versus 15-25 year old females in terms of HPV-16 and HPV-18 GMT ratios, one month post-dose three (ATP Cohort for Immunogenicity)

	Cervarix 3-dose Months 0, 1, 6)				GMT ratio (95% CI)
	Subjects 9-14 years		Subjects 15-25 years		
	N	GMT	N	GMT	Value (LL, UL)
Anti-HPV 16	67	22261.3	111	10322.0	2.16 (1.57, 2.97)
Anti-HPV 18	68	7398.8	114	4261.5	1.74 (1.32, 2.29)

Source: STN 125259.132.2, Module 5.3.5.1.3, Study HPV-048, Supplemental Report, table 2, p. 10

Table 9: Study HPV-048 – Non-inferiority of the anti-HPV 16 and anti-HPV 18 response to Cervarix in 9-14 year old females versus 15-25 year old females in terms of HPV-16 and HPV-18 GMT ratios, one month post-dose three (TVC Cohort for Immunogenicity)

	Cervarix 3-dose Months 0, 1, 6)				GMT ratio (95% CI)
	Subjects 9-14 years		Subjects 15-25 years		
	N	GMT	N	GMT	Value (LL, UL)
Anti-HPV 16	74	22348.2	126	9685.4	2.31 (1.70, 3.12)
Anti-HPV 18	74	7321.5	129	3999.2	1.83 (1.40, 2.40)

Source: STN 125259.132.2, Module 5.3.5.1.3, Study HPV-048, Supplemental Report, Supplement 1, p. 13

Reviewer's Comment: ***For both HPV-16 and HPV-18, GMTs are higher in the 9-14 year old group as compared to the 15-25 year old group, with the LB of the 95% CI around GMT ratio greater than 0.5. This is true for both the ATP cohort and TVC cohort for immunogenicity. GSK also provides seropositivity rates and GMTs by baseline serostatus for each of the two HPV types. In both age groups and both analysis cohorts, all subjects were seropositive at 1 month after dose 3 Cervarix, regardless of baseline serostatus. GMTs were higher in the younger subjects as compared to the older subjects in both cohorts and for both HPV types at 1 month after dose 3.***

Immunogenicity Conclusion: Non-inferiority of immune response to Cervarix in 9-14 year old females vs. 15-25 year old females with respect to anti-HPV-16 and anti-HPV-18 GMTs was demonstrated. Therefore, efficacy of Cervarix can be inferred in females 9-14 years of age based on this analysis.

SAFETY RESULTS

The primary evaluation of safety was assessed in the **Total Vaccinated Cohort (TVC)** for Groups 1 and 2. The total number of events were noted for all age groups, and also assessed for subjects 9-17 years of age and 18-25 years of age. Safety (solicited adverse events, unsolicited adverse events, serious adverse events, adverse events which led to discontinuation, new onset autoimmune diseases) was also reviewed in Groups 3 and 4 to evaluate whether there was any signal in the pediatric subjects who received any formulation of the HPV 16/18 AS04 vaccine.

Safety in Females 9 through 25 years of age: Safety data was reviewed from study HPV-048 in pediatric females 9 through 17 years of age and in adult females 18 through

25 years of age who received at least one dose of the licensed formulation of Cervarix. Further comparisons were made to the safety data from the larger studies in both age groups which supported the original approval of Cervarix in 2009. In addition, safety was assessed in subjects in those age strata who received the higher-dose formulation in order to rule out unexpected safety signals in all ages, but with focus on the pediatric subjects. From review of datasets provided for study HPV-048 (pid.xpt), the numbers of subjects in the pediatric and adult age groups are presented in Table 10 below. With this study, additional safety data is provided in 253 subjects 9-17 years of age who received any dose of the licensed formulation of Cervarix.

Table 10: Study HPV-048 - Number of subjects Enrolled by Group and Age Strata (9-17 years and 18-25 years) (CBER-generated)

Group	Dosage HPV 16/18 (μg) at Time of Administration	9-17 year olds	18-25 year olds
1	20/20 @ 0, 1, 6 months	128	111
2	20/20 @ 0, 6 months	125	115
	TOTAL who received at least one dose of licensed formulation	253	226
3	40/40 @ 0, 6 months	128	113
4	40/40 @ 0, 2 months	129	111
	TOTAL who received at least one dose of 40/40 formulation	257	224
	TOTAL who received any formulation of HPV 16/18 vaccine	510	450

Data from STN 125259/132, CSR HPV-048, Module 5.3.5.1.25.3.1 pid.xpt dataset

Safety was reviewed by age groups from the datasets provided. Proportions of subjects with solicited local and general adverse events days 0-6 after vaccination, unsolicited adverse events in the 30 days after vaccination, and serious adverse events were similar in the 9-17 years and 18-25 years age strata, and also were comparable to proportions reported in the original Cervarix package insert (9-14 in HPV-048 compared to original studies in 10-14 years and 15-25 years in HPV-048 compared to original studies in subjects 15-25 years of age). In study HPV-048, no serious adverse events were noted in subjects who were 9 years of age at the time of vaccination in any of the treatment groups.

Number and percentage of subjects who received active vaccine dose(s) (Total Vaccinated cohort) for Groups 1-4: 100% of subjects in the 3-dose and 2-dose group received any dose of vaccine, and 97.1% of the 3-dose group and 96.3% of the 2-dose group received all planned doses. In Group 3, 95.9% of all subjects received both doses and 100% of subjects received at least one dose. In Group 4, 97.5% of all subjects received both doses and 100% of subjects received at least one dose. (Source: STN 125259/132.2, Module 5.3.5.1.3, CSR HPV-048, Table 38, p. 107).

Solicited adverse events, local and general, in the 7 days after vaccination, Study HPV-048: Solicited symptoms in all 4 treatment groups were reviewed from safety datasets by specific age group. CBER compared incidences overall per subject in 9-17 year old subjects with those 18-25 years of age in Group 1(Table 11), in Group 2 (Table 12), and combined Groups 1 and 2 (Table 13).

Table 11: Study HPV-048 - Incidence and nature of symptoms (solicited) reported during the 7-day (Days 0-6) post-vaccination (with Cervarix) period overall/subject by *age group* (Total Vaccinated cohort – Group 1) [CBER generated]

	Any symptom		Local symptoms		General symptoms	
	n/N	%	n/N	%	n/N	%
Group 1 – 9-17 years :						
Any	124/128	96.9%	123/128	96.1%	96/128	75.0%
Grade 3	32/128	25.0%	22/128	17.2%	16/128	12.5%
Group 1 – 18-25 years:						
Any	107/111	96.4%	104/111	93.7%	80/111	72.1%
Grade 3	22/111	19.8%	17/111	15.3%	7/111	6.3%

N= number of subjects with at least one documented dose within reaccod.xpt dataset
n= number of subjects presenting at least one type of symptom whatever the study vaccine administered
%= percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: From STN 125259/132.1, Module 5.3.5.1.25.3.1, CSR HPV-048, REACCOD.XPT dataset

Table 12: Study HPV-048 - Incidence and nature of symptoms (solicited) reported during the 7-day (Days 0-6) post-vaccination (with Cervarix) period overall/subject by *age group* (Total Vaccinated cohort – Group 2) [CBER generated]

	Any symptom		Local symptoms		General symptoms	
	n/N	%	n/N	%	n/N	%
Group 2 – 9-17 years :						
Any	120/125	96.0%	118/125	94.4%	95/125	76.0%
Grade 3	27/125	21.6%	21/125	16.8%	19/125	15.2%
Group 2 – 18-25 years:						
Any	108/115	93.9%	105/115	91.3%	90/115	78.3%
Grade 3	9/115	7.8%	7/115	6.1%	4/115	3.5%

N= number of subjects with at least one documented dose within reaccod.xpt dataset
n= number of subjects presenting at least one type of symptom whatever the study vaccine administered
%= percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: From STN 125259/132.1, Module 5.3.5.1.25.3.1, CSR HPV-048, REACCOD.XPT dataset

Table 13: Study HPV-048 - Incidence and nature of symptoms (solicited) reported during the 7-day (Days 0-6) post-vaccination (with Cervarix) period overall/subject by *age group* (Total Vaccinated cohort – Groups 1 and 2 combined) [CBER generated]

	Any symptom		Local symptoms		General symptoms	
	n/N	%	n/N	%	n/N	%
Groups 1 and 2 – 9-17 years :						
Any	244/253	96.4%	241/253	95.3%	191/253	75.5%
Grade 3	59/253	23.3%	43/253	17.0%	32/253	12.6%
Groups 1 and 2 – 18-25 years:						
Any	215/226	95.1%	209/226	92.5%	170/226	75.2%
Grade 3	31/226	13.7%	24/226	10.6%	11/226	4.9%

N= number of subjects with at least one documented dose within reaccod.xpt dataset
n= number of subjects presenting at least one type of symptom whatever the study vaccine administered
%= percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: From STN 125259/132.1, Module 5.3.5.1.25.3.1, CSR HPV-048, REACCOD.XPT dataset
[combined totals for Groups 1 and 2]

CBER also reviewed solicited adverse events from the reaccod.xpt dataset (STN 125259/132.1, Module 5.3.5.1.25.3.1) in Group 3 and Group 4 subjects, combined, for the 9-17 years and the 18-25 years of age strata. Findings were similar to those noted for combined Groups 1 and 2.

Reviewer's Comment: ***A higher proportion (12.6%) of the combined younger age group experienced a Grade 3 solicited general symptom within 7 days after any vaccination (12.6%)***

as compared to subjects 18-25 years of age (4.9%). To investigate the differences identified, comparisons were made to original data from studies HPV-013 and HPV-008 for all solicited adverse events, as well as review of specific solicited local and general adverse events within study HPV-048.

Solicited adverse events, local and general, in the 7 days after vaccination, Study HPV-048 (15-25 years and 9-14 years) compared to Studies HPV-008 (ages 15-25 years) and HPV-013 (ages 10-14 years), respectively: In the studies which supported original licensure, safety and efficacy studies were conducted in subjects 15-25 years of age and safety and immunogenicity were assessed in subjects 10-14 years of age.

CBER made observational comparisons for solicited adverse events in the 7 days after vaccination (overall/subject) between subjects 9-14 years of age and 15-25 years of age in Group 1 (study HPV-048) and subjects who participated in the pivotal efficacy studies and were included in the Diary Card subset of HPV-008 (15-25 years of age) and pediatric subjects who participated in study HPV-013 (10-14 years of age). The results are shown in Table 14 with observational comparisons to the original data for each age group.

- There was a higher proportion of subjects 9-14 years of age in study HPV-048 with local solicited symptoms in the 7 days after vaccination (98%) as compared to the proportions of subjects 10-14 years of age in study HPV-013 (87.5%). There was little difference, however, in the proportion of grade 3 local adverse events in these two groups (16.0% HPV-048 and 14.4% HPV-013).
- For Grade 3 general solicited adverse events, there was little difference in incidence rates overall per subject in subjects 9-14 years of age in study HPV-048 (13.0%) and in subjects 10-14 years of age in study HPV-013 (14.2%). Further, in study HPV-008 in subjects 15-25 years of age, the incidence rate of Grade 3 general adverse events was 11.5%, and therefore very similar to the rates noted for the younger group in both HPV-048 and HPV-013.

Reviewer's Comment: Studies HPV-008 and HPV-013 were controlled, randomized, double-blind studies in which safety of Cervarix was compared to an active control (Hepatitis A virus vaccine, either 720 IU/0.5mL for subjects 15-25 years and 360 IU/0.5mL for subjects 10-14 years of age). In addition, the sample size of study HPV-048 was smaller as compared to the original pivotal studies and the comparisons were made in a post-hoc fashion, so such comparisons must be interpreted with caution since they were post-hoc in nature, sample sizes were different in the studies involved, and the additional 9-25 year old subjects were not part of the same controlled studies.

Table 14: Incidence and nature of symptoms (solicited) reported during the 7-day (Days 0-6) post-vaccination (with Cervarix) period overall/subject in Group 1 (study HPV-048) by *age group and compared to subjects in HPV-008 [15-25] and HPV-013[10-14]* [CBER generated]

	Any symptom		Local symptoms		General symptoms	
	n/N	%	n/N	%	n/N	%
Study HPV-048:						
Group 1 – 9-14 years : Any	80/82	98.0%	80/82	98.0%	61/82	74.0%
Group 1 – 9-14 years: Grade 3	20/82	24.0%	13/82	16.0%	11/82	13.0%
Study HPV-013						
10-14 years: Any	954/1029	92.7%	900/1028	87.5%	820/1029	79.7%
10-14 years: Grade 3	226/1029	22.0%	148/1028	14.4%	146/1029	14.2%
	n/N	%	n/N	%	n/N	%
Study HPV-048:						
Group 1 – 15-25 years: Any	151/157	96.0%	147/157	94.0%	115/157	73.0%
Group 1 – 15-25 years: Grade 3	34/157	22.0%	26/157	17.0%	12/157	8.0%
Study HPV-008*						
15-25 years: Any	2862/3077	93.0%	2805/3077	91.2%	2426/3076	78.9%
15-25 years: Grade 3	731/3077	23.8%	560/3077	18.2%	355/3076	11.5%

Study HPV-048: N= number of subjects with at least one documented dose within reaccod.xpt dataset
n=number of subjects presenting at least one type of symptom whatever the study vaccine administered
%=percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
*Study HPV-008 – subjects in Diary Card subset from original application
Study HPV-013 – subjects 10-14 years of age who received Cervarix formulation
Source: From STN 125259/132.1, Module 5.3.5.1.25.3.1, CSR HPV-048, REACCOD.XPT dataset ; STN 125259.0048, CSR 008, Supplements 298 - 299, p. 10501-2 ; STN 125259/0, Module 5.3.5.1.3, CSR HPV-013, Supplement s 11-12, p. 103-4

Solicited Local Adverse Events in the 7 days after any vaccination, Study HPV-048, subjects 9-17 years compared to subjects 18-25 years: Solicited local adverse events were pain, redness and swelling in the 7 days after any vaccination.

Duration of Local symptoms: Pain and swelling lasted a little over three days, and swelling lasted approximately 3 days. The duration of Grade 3 pain, redness and swelling, when it occurred, was short in duration (app. 1-2 days).

To assess proportions of solicited local adverse events in the pediatric group (9-17 years) and adult group (18-25 years) in subjects who received any dose of the licensed formulation of vaccine, CBER tabulated the solicited specific local symptoms by each age group in Group 1 (Table 15) and group 2 (Table 16) (overall/subject) from the reaccod.xpt datasets.

Table 15: Study HPV-048 - Incidence of any and grade 3 solicited local symptoms [Pain, redness, Swelling] reported during the 7-day (Days 0-6) post-vaccination (with Cervarix) period overall/subject by Age Strata (9-17 years and 18-25 years) (Total Vaccinated cohort – Group 1)[CBER generated]

Treatment	Age Strata (yrs)	Pain	Grade 3 pain	Redness	Grade 3 redness	Swelling	Grade 3 swelling
		n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Group 1 20µg HPV-16/ 20µg HPV-18 @M0, 1, 6	**9-17 (N=128)**	118/128 (92.2%)	19/128 (14.8%)	86/128 (67.2%)	2/128 (1.6%)	63/128 (49.2%)	4/128 (3.1%)
	18-25 (N=125)	103/111 (92.8%)	15/111 (13.5%)	54/111 (48.6%)	1/111 (0.9%)	53/111 (51.4%)	1/111 (0.9%)

N= number of subjects with at least one documented dose
n=number of subjects presenting at least one type of symptom whatever the study vaccine administered
%= percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: STN 125259/132.1, Module 5.3.5.1.25.3.1, CSR HPV-048 reaccod.xpt dataset

Table 16: Study HPV-048 - Incidence of any and grade 3 solicited local symptoms [Pain, redness, Swelling] reported during the 7-day (Days 0-6) post-vaccination(with Cervarix) period overall/subject by Age Strata (9-17 years and 18-25 years) (Total Vaccinated cohort – Group 2)[CBER generated]

Treatment	Age (yrs)	Pain	Grade 3 pain	Redness	Grade 3 redness	Swelling	Grade 3 swelling
		n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Group 2 20µg HPV-16 /20µg HPV-18 @ M0, 6	**9-17 (N=125)**	116/125 (92.8%)	18/125 (14.4%)	54/125 (43.2%)	1/125 (0.8%)	35/125 (28%)	1/125 (0.8%)
	18-25 (N=115)	105/115 (91.3%)	7/115 (6.1%)	70/115 (60.9%)	0/115 (0%)	49/115 (42.6%)	1/115 (0.9%)

N= number of subjects with at least one documented dose
n=number of subjects presenting at least one type of symptom whatever the study vaccine administered
%= percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: STN 125259/132.1, Module 5.3.5.1.25.3.1, CSR HPV-048, reaccod.xpt dataset

Reviewer's Comment:
In Group 1, a higher proportion of subjects 9-17 years experienced redness (67.2%) in the 7 days after vaccination as compared to older females (48.6%), although rates of grade 3 redness were generally comparable in the two age groups (1.6% in subjects 9-17 years and 0.9% in subjects 18-25 years of age). In addition, in review of the reaccod.xpt datasets, no clustering of these events of redness in the youngest subjects was identified. The two grade 3 events of redness identified in the reaccod.xpt dataset occurred in subjects 14 and 16 years of age (not in the 9 year old subjects).

In Group 2, a higher proportion of pediatric subjects experienced grade 3 pain as compared to the adult group, although a higher proportion of adults experienced redness and swelling compared to the pediatric group, which were not noted for comparisons in Group 1. In review of the reaccod.xpt dataset, Grade 3 pain was distributed throughout the pediatric age group.

The vast majority of subjects in all studies received the full course of vaccination, so any differences in frequency of local solicited adverse events in study HPV-048 between age groups did not appear to impact on completion rate of the planned vaccination series. As noted in the package insert and at the time of initial approval, local adverse events occurred in

a higher proportion of Cervarix recipients as compared to subjects who received the active control, Havrix, for both age groups.

Overall tabulated rates for specific solicited local adverse events by age strata in combined Groups 1 and 2 (those who received any dose of licensed formulation of Cervarix) are shown in Table 17.

Table 17: Study HPV-048 - Incidence of any and grade 3 solicited local symptoms [Pain, redness, Swelling] reported during the 7-day (Days 0-6) post-vaccination (with Cervarix) period overall/subject by Age Strata (9-17 years and 18-25 years) (Total Vaccinated cohort – Group 1 and Group 2)[CBER generated]

Treatment	Age (yrs)	Pain	Grade 3 pain	Redness	Grade 3 redness	Swelling	Grade 3 swelling
		n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Group 1 and Group 2 combined	**9-17 (N=253)**	234/253 (92.5%)	37/253 (14.5%)	140/253 (55.3%)	3/253 (1.2%)	98/253 (38.7%)	5/253 (2.0%)
	18-25 (N=226)	208/226 (92.0%)	22/226 (9.7%)	139/226 (61.5%)	1/226 (0.4%)	102/226 (48.2%)	2/226 (0.9%)

N= number of subjects with at least one documented dose
n=number of subjects presenting at least one type of symptom whatever the study vaccine administered
%= percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: STN 125259/132, Module 5.3.5.1.25.3.1, CSR HPV-048, reaccod.xpt dataset

Reviewer's Comment: As noted in Table 17, when Groups 1 and 2 data for specific local reactions are combined, a higher proportion of 9-17 year old subjects experienced grade 3 pain (14.5%) as compared to the 18-25 year old age group (9.7%). In review of the reaccod.xpt datasets, individual grade 3 events were identified and found to be distributed throughout all pediatric-age subjects. No clustering of events was noted in the youngest subjects. The proportions of subjects experiencing local pain, redness and grade 3 redness, and swelling and grade 3 swelling were comparable between the younger and older age groups. No impact on study completion was observed due to the slight difference in Grade 3 pain.

In light of this, the higher proportion of solicited local symptoms noted in the younger subjects in Table 13 for combined subjects (Groups 1 and 2) appeared to be at least partially due to a higher proportion of younger subjects from Group 2 experiencing Grade 3 pain (difference not seen in Group 1) and a higher proportion of younger subjects with any redness in Group 1 (although a higher proportion of redness was noted in the older age seen in Group 2). Differences were not consistent across groups.

Specific solicited local adverse events in the 7 days after vaccination, Study HPV-048 (15-25 years of age and 9-14 years of age) compared to Studies HPV-008 (15-25 years of age) and HPV-013 (10-14 years of age): CBER also reviewed solicited local symptoms (any or grade 3) in subjects who participated in study HPV-048 (Group 1) and in studies which supported initial licensure of Cervarix. The incidences of specific local symptoms are shown in Table 18.

Table 18: Incidence of any and grade 3 solicited local symptoms [Pain, redness, Swelling] reported overall/subject during the 7-day (Days 0-6) post-vaccination period (with Cervarix) in Group 1 (study HPV-048) by *age group and compared to subjects in HPV-008 [15-25] and HPV-013[10-14]* [CBER generated]

	Age (yrs)	Pain	Grade 3 pain	Redness	Grade 3 redness	Swelling	Grade 3 swelling
		n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Study HPV-048	**9-14 (N=82)**	77/82 94.0%	12/82 15.0%	57/82 70.0%	1/82 1.0%	39/82 48.0%	1/82 1.0%
Study HPV-013	**10-14 (N=1028)**	888/1028 86.4%	116/1028 11.3%	466/1028 45.3%	11/1028 1.1%	430/1028 41.8%	30/1028 2.9%
Study HPV-048	**15-25 (N=157)**	144/157 92.0%	22/157 14.0%	83/157 53.0%	2/157 1.0%	77/157 49.0%	4/157 3.0%
Study HPV-008	**15-25 (N=3077)**	2786/3077 90.5%	502/3077 16.3%	1348/3077 43.8%	37/3077 1.0%	1292/3077 42.0%	74/3077 2.4%

Study HPV-048: N= number of subjects with at least one documented dose within reaccod.xpt dataset
n=number of subjects presenting at least one type of symptom whatever the study vaccine administered
%= percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
*Study HPV-008 – subjects in Diary Card subset from original application and Study HPV-013 – subjects 10-14 years of age who received Cervarix formulation (STN 125259/0); Source: STN 125259/132.1, Module 5.3.5.1.25.3.1, CSR HPV-048 reaccod.xpt dataset and STN 125259/0, Module 5.3.5.1.3, CSR HPV-013, Table 24, p. 71 and STN 125259.0048, Module 5.1.5.1.3, CSR 008, Table 104, p. 366-367

Reviewer's Comment: The higher proportions of subjects with specific local adverse events were observed in both the younger and older age groups in study HPV-048 as compared to those subjects in studies HPV-013 and HPV-008, respectively. The highest numeric differences was noted in any redness in the younger age groups (70.0% in study HPV-048 and 45.3% in study HPV-013), although there was no difference in proportion of younger subjects with Grade 3 redness (1.0% in study HPV-048 and 1.1% in study HPV-013). In review of the reaccod.xpt dataset for study HPV-048, redness was distributed across the 9-14 year old age range. Other comparisons were generally comparable.

Solicited General Adverse Events in 7 days post-vaccination, Study HPV-048:
Solicited general symptoms in the 7 days after vaccination included arthralgia, fatigue, fever, gastrointestinal symptoms, headache, myalgia, rash, and urticaria. Overall, after HPV vaccine doses, headache, fatigue and myalgia were the most often reported solicited general symptoms.

Groups 1 and 2 are presented separately by age group (Table 19) and combined by each age group (Table 20).

Within **Group 1**, CBER assessed the solicited general adverse events according to age strata (9-17 years and 18-25 years) in subjects who received at least one dose of the licensed formulation of Cervarix (Groups 1 and 2). The proportions of subjects with at least one specific solicited adverse event are shown in Table 19.

Table 19: Study HPV-048 - Incidence of any solicited general adverse events reported during the 7-day (Days 0-6) post-vaccination (with Cervarix) period overall/subject by Age Strata (9-17 years and 18-25 years) (Total Vaccinated cohort – Group 1 and Group 2) [CBER generated]

	Group 1 (20/20 @ M0, 1, 6)		Group 2 (20/20 @ M0, 6)	
General adverse event	**9-17 years of age N=128**	**18-25 years of age N=111**	**9-17 years of age N=125**	**18-25 years of age N=115**
	n(%)	n (%)	n (%)	n (%)
Arthralgia	22 (17.2%)	18 (16.2%)	25 (20%)	16 (13.9%)
Grade 3 Arthralgia	2 (1.6%)	1 (0.9%)	3 (2.4%)	1 (0.9%)
Fatigue	58 (45.3%)	48 (43.2%)	58 (46.4%)	54 (47%)
Grade 3 Fatigue	5 (3.9%)	3 (2.7%)	6 (4.8%)	1 (0.9%)
Fever	24 (18.8%)	16 (14.4%)	18 (14.4%)	10 (8.7%)
Fever 39.1-41.1˚C	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Gastrointestinal	37 (28.9%)	31 (27.9%)	23 (18.4%)	22 (19.1%)
Grade 3 Gastrointestinal	4 (3.1%)	3 (2.7%)	3 (2.4%)	0 (0.0%)
Headache	68 (53.1%)	54 (48.6%)	62 (49.6%)	59 (51.3%)
Grade 3 Headache	10 (7.8%)	3 (2.7%)	7 (5.6%)	2 (1.7%)
Myalgia	44 (34.4%)	54 (48.6%)	50 (40%)	52 (45.2%)
Grade 3 Myalgia	4 (3.1%)	2 (1.8%)	6 (4.8%)	0 (0.0%)
Rash	12 (9.4%)	3 (2.7%)	7 (5.6%)	9 (7.8%)
Grade 3 Rash	1 (0.8%)	0 (0.0%)	1 (0.8%)	0 (0.0%)
Urticaria	2 (1.6%)	3 (2.7%)	3* (2.4%)	2 (1.7%)
Grade 3 urticaria	0 (0.0%)	0 (0.0%)	3 (2.4%)	0 (0.0%)

N=number of subjects with at least one dose;
n=number of subjects with at least one specific solicited general adverse event
% = percentage of subjects with at least one specific solicited general adverse event
*1/3 urticarial events occurred after administration of aluminum hydroxide dose
Source: STN 125259/132.1, Module 5.3.5.1.25.3.1, CSR HPV-048, reaccod.xpt dataset

Table 20: Study HPV-048 - Incidence of any and grade 3 solicited general adverse events reported during the 7-day (Days 0-6) post-vaccination (with Cervarix) period overall/subject by Age Strata (9-17 years and 18-25 years) (Total Vaccinated cohort – Group 1 plus Group 2 combined) [CBER generated]

	Group 1 plus Group 2 combined	
General adverse event	**9-17 years N=253**	**18-25 years N=226**
	n (%)	n (%)
Arthralgia	47 (18.6%)	34 (15.0%)
Grade 3 Arthralgia	5 (2.0%)	2 (0.9%)
Fatigue	116 (45.8%)	112 (50%)
Grade 3 Fatigue	11 (4.3%)	4 (1.8%)
Fever	42 (16.6%)	26 (11.5%)
Fever 39.1-41.1˚C	0 (0.0%)	1 (0.4%)
Gastrointestinal	60 (23.7%)	53 (23.5%)
Grade 3 Gastrointestinal	7 (2.8%)	3 (1.3%)
Headache	130 (51.4%)	113 (50%)
Grade 3 Headache	17 (6.7%)	5 (2.2%)
Myalgia	94 (37.2%)	106 (46.9%)
Grade 3 Myalgia	10 (4.0%)	2 (0.9%)
Rash	19 (7.5%)	12 (5.3%)
Grade 3 Rash	2 (0.8%)	0 (0.0%)
Urticaria	5 (2.0%)	5 (2.2%)
Grade 3 urticaria	1 (0.4%)	0 (0.0%)

N=number of subjects with at least one dose;
n=number of subjects with at least one specific solicited general adverse event
%=percentage of subjects with at least one specific solicited general adverse event
Source: STN 125259/132.1, Module 5.3.5.1.25.3.1, CSR HPV-048, reaccod.xpt dataset

Reviewer's Comment: In Group 1, the proportions of subjects reporting any solicited general adverse events were generally comparable in the two age groups (9-17 years and 18-25 years of age). However, a higher proportion of younger subjects experienced any arthralgia, fatigue, fever and rash as compared to the 17-25 year old age group, and a higher proportion of older subjects experienced any gastrointestinal events, headache, and myalgia as compared to younger subjects.

In Group 2, a higher proportion overall of subjects 9-17 years of age experienced any arthralgia and fever as compared to subjects 18-25 years of age, while a higher proportion of subjects 18-25 years of age experienced any fatigue, gastrointestinal events, and myalgia as compared to the younger age group. These differences in rates did not appear to correlate with differences in proportions of subjects who discontinued due to an adverse event.

Overall, Grade 3 events occurred in ≤7.8% of subjects in both age groups in either Group 1 or Group 2 in study HPV-048. Higher proportions of Grade 3 arthralgia, Grade 3 fatigue, Grade 3 headache and Grade 3 myalgia were reported in the 9-17 year old subjects as compared to subjects 18-25 year old subjects.

Grade 3 adverse events are discussed below.

- **Grade 3 arthralgia:** In combined groups 1 and 2, the 9-17 year old subjects had higher incidence rates of Grade 3 arthralgia as compared to 15-25 year old subjects in study HPV-048. These events were reviewed from the reaccod.xpt datasets. Subjects were aged 13 years (1 subject), 14 years (2 subjects), 15 years (1 subject) and 16 years (1 subject). All five subjects had arthralgia which lasted 1-2 days, occurred after various doses (1, 2, and 3), 4/5 assesed as related, and all resolved.
- **Grade 3 fatigue:** In combined groups 1 and 2, the 9-17 year old subjects had higher incidence rates of Grade 3 fatigue as compared to 15-25 year old subjects in study HPV0-048. These 11 events were reviewed from the reaccod.xpt datasets. Subjects were aged 10 years (1 subject), 11 years (1 subject), 12 years (2 subjects), 13 years (3 subjects), 14 years (1 subject), 15 years (1 subject), 16 years (1 subject), and 17 years (1 subject). These 10 subjects had fatigue which lasted 1-5 days total (9/10 lasted for 1-2 days), occurred after various doses (including 2 subjects who experienced grade 3 fatigue after the dose of alum), the majority were assessed as related to study material, and all events resolved.
- **Grade 3 Headaches:** Higher proportions of younger subjects in both Groups 1 and 2 experienced Grade 3 headaches as compared to subjects 18-25 years of age. The reaccod.xpt datasets were reviewed for subjects in each age group who experienced a headache and grade 3 headache to ascertain the age distribution and outcomes. Of the 10 grade 3 headaches reported in Group 1 in the 9-17 year old age group, the age distribution with duration was as follows: one at age 11 [1 day], two at age 12 [1 day and 2 days], one at age 13 [1 day], one at age 14 [1 day], three at age 16 [1 day and 2 days for one subject, and 1 day for each of the other two subjects] and two at age 17 [2 days each subject]. Of the seven reported in subjects 9-17 years of age in Group 2, two occurred at age 13 [2 days and 3 days, three at age 14 [1 day severe on D0, mild-moderate other days], 2 days and 1 day], and 2 occurred at age 15 [1 day and 2 days]. The subject who was 14 years old from Group 2 who developed a headache for total 30 days after dose 3 in the series was reviewed in further detail. The headache was described as being Grade 3 in intensity for one day and was graded as mild to moderate on the other days. This subject was noted to develop an URI/nasopharyngitis which started at 27 days after dose 3 of the series (and overlapped with headache). This subject had mild headache after dose 1 Cervarix on 2 days and mild – moderate headache after dose 2 series (alum) x 4 days. In review of wmedic.xpt dataset to review medications taken, this subject took 650 mg acetominophen for 2 days (4/1 and 4/2/08, which was day of vaccination and day after) as well as 975 mg acetaminophen for 3 days (4/27-4/29/08) as well as cold medicine for 4 days (4/28 – 5/1/08). The latter two medications correlated with occurrence of URI/nasopharyngitis.

Reviewer's Comment: The grade 3 events occurred throughout the pediatric age group, were not concentrated in the youngest subjects who received the licensed Cervarix formulation, the majority of subjects had events of short duration (1-3 days), and all resolved.

- **Grade 3 myalgia:** In combined groups 1 and 2, the 9-17 year old subjects had higher incidence rates of Grade 3 myalgia as compared to 15-25 year old subjects in study HPV-048. These 10 events were reviewed from reaccod.xpt datasets. Subjects were aged 11 years (1 subject), 12 years (2 subjects), 13 years (2 subjects), 14 years (3 subjects), and 16 years (2

subjects). In these 10 subjects, myalgia lasted 1-5 days (9/10 lasted 1-2 days), occurred after various doses of Cervarix (and 1/10 occurred after receipt of alum lasting 5 days), the majority were assessed as related to study material, and all resolved.

Reviewer's Comment: Although the younger subjects in study HPV-048 had higher rates of Grade 3 arthralgia, fatigue, headache, and myalgia in the seven days after any vaccination, the duration of most of these events was short (the majority lasting 1-2 days long), and those subjects who were to receive additional doses of vaccine went onto to receive the vaccine without recurrence of the Grade 3 solicited general adverse events.

Two other data sources considered in assessing the rates of these Grade 3 solicited general adverse events in younger and older subjects included post-marketing safety update reports (provided through November 2010), and review of Grade 3 general solicited adverse events in studies HPV-013 and HPV-008.

- From post-marketing safety update reports to date, the reporting rate of headaches overall in subjects 9-17 years of age (4.18/100,000) was lower as compared to all subjects (5.28/100,000) in the post-marketing period (Table 25). In addition, the reporting rates were lower for all fatigue (1.02/100,000 in younger group) as compared to all subjects (1.44/100,000), as well as for all myalgia (0.93/100,000 in subjects 9-17 years) as compared to all subjects (1.66/100,000).
- Solicited general adverse events in the 7 days after vaccination for study HPV-048 for subjects 9-14 years of age, subjects 15-25 years of age, subjects 10-14 years of age in study HPV-013, and subjects 15-25 years of age in study HPV-008, respectively. These comparisons are presented below.

  Solicited general adverse events in the 7 days after vaccination, Study HPV-048 (15-25 years of age and 9-14 years of age) compared to Studies HPV-008 (15-25 years of age) and HPV-013 (10-14 years of age): When proportions of subjects with solicited general adverse events are compared to proportions of subjects 10-25 years of age who participated in studies which supported initial licensure of Cervarix, the proportions are very similar to those in the younger and older age groups from Group 1. These observational comparisons are shown in Table 21.

Table 21: Incidence of any and grade 3 solicited general adverse events reported during the 7-day (Days 0-6) post-vaccination period (with Cervarix) overall/subject in Group 1 (study HPV-048) by *age group and compared to subjects in HPV-008 [15-25] and HPV-013[10-14]* [CBER generated]

	Study HPV-048 9-14 years N=82	Study HPV-013 10-14 years N=1029	Study HPV-048 15-25 years N=157	Study HPV-008* 15-25 years N=3076
General Adverse Event	n (%)	n (%)	n (%)	n (%)
Arthralgia	15 (18.3%)	259 (25.2%)	25 (15.9%)	633 (20.6%)
Grade 3 Arthralgia	2 (2.4%)	21 (2.0%)	1 (0.6%)	32 (1.0%)
Fatigue	35 (42.7%)	499 (48.5%)	71 (45.2%)	1771 (57.6%)
Grade 3 Fatigue	4 (4.9%)	40 (3.9%)	4 (2.5%)	126 (4.1%)
Fever	15 (18.3%)	193 (18.8%)	25 (15.9%)	381 (12.4%)
Fever 39.1-41.1˚C	0 (0%)	19 (1.8%)	0 (0.0%)	18 (0.6%)
Gastrointestinal	25 (30.5%)	265 (25.8%)	43 (27.4%)	850 (27.6%)
Grade 3 Gastrointestinal	2 (2.4%)	26 (2.5%)	5 (3.2%)	60 (2.0%)
Headache	40 (48.8%)	516 (50.1%)	82 (52.2%)	1665 (54.1%)
Grade 3 Headache	5 (6.1%)	68 (6.6%)	8 (5.1%)	131 (4.3%)
Myalgia	31 (37.8%)	509 (49.5%)	67 (42.7%)	1606 (52.2%)
Grade 3 Myalgia	4 (4.9%)	57 (5.5%)	2 (1.3%)	141 (4.6%)
Rash	9 (11.0%)	98 (9.5%)	6 (3.8%)	312 (10.1%)
Grade 3 Rash	1 (1.2%)	8 (0.8%)	0 (0.0%)	8 (0.3%)
Urticaria	2 (2.4%)	70 (6.8%)	3 (1.9%)	298 (9.7%)
Grade 3 urticaria	0 (0%)	9 (0.9%)	0 (0.0%)	29 (0.9%)

Study HPV-048: N= number of subjects with at least one documented dose within reaccod.xpt dataset
n= number of subjects presenting at least one type of symptom whatever the study vaccine administered
%=percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
*Study HPV-008 – subjects in Diary Card subset from original application
Study HPV-013 – subjects 10-14 years of age who received Cervarix formulation
Source: STN 125259/132.1, Module 5.3.5.1.25.3.1, CSR HPV-048 reaccod.xpt dataset; STN 125259.0048, CSR 008, Table 107, p. 371-375 and STN 125259/0, CSR HPV-013, Table 25, p. 72-74

Reviewer's Comment: When proportions of solicited general adverse events in study HPV-048 are compared in subjects 9-14 years of age to subjects 10-14 years of age in study HPV-013, no appreciable difference was observed as to overall incidence of solicited general adverse events or solicited general Grade 3 adverse events. In addition, comparable results were noted for subjects 15-25 years of age in studies HPV-048 and HPV-008. The solicited general adverse events were also reviewed (Source: STN 125259/132.1, Module 5.3.5.1.25.3.1, CSR HPV-048, reaccod.xpt dataset) for Groups 3 and 4 (40µg HPV-16/40µg HPV-18 @ Months 0, 6 and 40µg HPV-16/40µg HPV-18 @ Months 0, 2) by age strata, and proportions of subjects with specific solicited general adverse events overall per dose and overall per subject (any and grade 3) were similar to those as noted for subjects in Groups 1 and 2 for the 9-17 years and 18-25 year old age strata.

After review of the above data in totality, grade 3 solicited general adverse events which were experienced by pediatric subjects in study HPV-048 who received at least one dose of the licensed Cervarix formulation were short in duration, did not impact on completion rates of the vaccination series, and results in study HPV-048 for 9-14 year old subjects was similar to those noted in subjects 10-14 years of age in study HPV-013, as well as in subjects 15-25 years of age in study HPV-008.

Urticaria – Urticaria within 30 minutes was to be reported in all cases. No events of urticaria were identified in the wurti.xpt dataset, which included those events which occurred within 30 minutes. However, as noted in the package insert, urticaria has been reported to occur in 7.2% of subjects in the safety dataset within seven days of vaccination in subjects 9-25 years of age. Although this rate is similar to the rate of urticaria within 7 days after Havrix adult dose (7.9%) and Havrix pediatric dose (5.4%), CBER reviewed cases of urticaria within 7 days of vaccination.

CBER reviewed the datasets for the 5 subjects in Group 1, the 5 subjects in Group 2, the 5 subjects in Group 3, and the 4 subjects in Group 4 who experienced urticaria in the 7 days after any vaccination. The majority of these events were classified as mild. The ages of the subjects included one subject in each of the 10, 11, 18 and 25 year old age groups; 2 subjects each in the 12, 13, 20, 21, 23, and 24 year old age group; and 3 subjects in the 14 year old age group. Considering Groups 2 and 3, in which aluminum hydroxide was included as one dose of the series, one subject in Group 2 developed urticaria after receipt of aluminum hydroxide placebo (given as dose 2 in this regimen). Except for one subject in Group 1 who developed the event after dose 3 Cervarix, all other subjects who developed urticaria went onto receive either one or two additional doses of Cervarix without further episodes of urticaria. In Groups 3 and 4, six of the nine events were considered vaccine related. Eight of the nine events were mild in intensity, the other moderate. Three of the nine occurred after dose 3; four of the nine received another dose of HPV vaccine after the initial event without reported recurrence; one of the nine received a dose of alum after the event occurred after dose 2 of HPV vaccine; and one of the nine did not receive additional dose of any vaccine. All events resolved.

Reviewer's Comment: Review of urticaria events after receipt of the US-approved formulation of Cervarix (i.e., 20µg HPV-16/20µg HPV-18) within seven days of vaccination demonstrated that the majority of these events were mild in intensity, occurred after any dose of study vaccine (including aluminum hydroxide), occurred throughout all ages, and except for one subject did not prevent administration of further doses of study vaccine. A similar pattern was noted in subjects who received the higher dose formulation of vaccine.

Unsolicited Adverse Events in 30 days post-vaccination, Study HPV-048: Unsolicited adverse events were reported in the 30 days after each vaccination. These events are presented by age strata for Groups 1 and 2 combined in Table 22.

Table 22: Study HPV-048 - Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class within the 30-day (Days 0-29) post-vaccination period following each HPV vaccine dose by Age Strata (9-17 years and 18-25 years) (Total Vaccinated cohort – Group 1 combined with Group 2) [CBER generated]

	Groups 1 and 2 (20µg HPV-16/20µg HPV-18 @ M0, 1, 6 and @M0, 6)	
	9-17 years	18-25 years
	N=253	N=226
Primary System Organ Class	n/%	n/%
At least one symptom	130/51.4%	100/44.2%
At least one grade 3 symptom	16 /6.3%	16 /7.1%
Blood and lymphatic system disorders	0/0.0%	0/0.0%
Cardiac disorders	0/0.0%	0/0.0%
Ear and labyrinth disorders	5/2.0%	1/0.4%
Endocrine disorders	1/0.4%	1/0.4%
Eye disorders	0/0.0%	1/0.4%
Gastrointestinal disorders	16/6.3%	8/3.5%
General disorders and administration site conditions	25/9.9%	25/9.9%
Hepatobiliary disorders	0/0.0%	2/0.9%
Immune system disorders	3/1.2%	0/0.0%
Infections and Infestations	57/22.5%	38/16.8%
Injury, poisoning and procedural complications	15/5.9%	7/3.1%
Investigations	0/0.0%	0/0.0%
Metabolism and nutrition disorders	3/1.2%	0/0.0%
Musculoskeletal and connective tissue disorders	16/6.3%	6/2.7%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1/0.4%	0/0.0%
Nervous system disorders	15/5.9%	15/6.6%
Psychiatric disorders	5/2.0%	5/2.2%
Renal and urinary disorders	0/0.0%	0/0.0%
Reproductive system and breast disorders	6/2.4%	7/3.1%
Respiratory, thoracic and mediastinal disorders	17/6.7%	10/4.4%
Skin and subcutaneous tissue disorders	8/3.2%	7/3.1%
Surgical and medical procedures	1/0.4%	0/0.0%
Vascular disorders	1/0.4%	3/1.3%

Source: STN 125259/132.1, Module 5.3.1.25.3.1, CSR HPV-048, wunsol.xpt dataset and pid.xpt

Reviewer's Comment: Within study HPV-048, overall, the proportions of subjects reporting an unsolicited adverse event within 30 days after any vaccination were higher in subjects 9-17 years of age as compared to subjects 18-25 years. This difference appears to be partially explained by an increased incidence of infections within 30 days of vaccination. In review of the reaccod.xpt dataset, these included common infections, such as ear infection, gastroenteritis, nasopharyngitis, influenza, otitis externa and otitis media, upper respiratory infection, urinary tract infection, exacerbation of HSV I infection. In the 9-17 year old age group, none of these infections were assessed as being serious in nature. In additional review of unsolicited adverse events for combined groups 3 and 4 by age strata (Source: STN 125259/132.1, Module 5.3.1.25.3.1, CSR HPV-048, wunsol.xpt dataset and pid.xpt), no additional issues of concern were identified.

In addition, the wunsol.xpt dataset was reviewed and grade 3 unsolicited adverse events were tabulated for each treatment group. These are included in Appendix 1 for full information (Tables A7-A10). In review of these Grade 3 unsolicited adverse events, the vast majority were assessed as unrelated to study vaccine, and most subjects recovered. In addition, if the event occurred after dose 1 or dose 2 of the series, most subjects went onto receive the full series. In Groups 2, 3 and 4, subjects also received aluminum hydroxide as part of the series, and some of the grade 3 adverse events occurred after receipt of the aluminum hydroxide dose.

Unsolicited adverse events in the 30 days after vaccination, Study HPV-048 compared to Studies HPV-008 and HPV-013: Unsolicited adverse events in subjects 9-14 years of age in Group 1 in study HPV-048 were compared with those reported by subjects 10-14 years of age in study HPV-013 (days 0-29). Similarly, proportions of subjects 15-25 years of age with unsolicited adverse events were compared from those in Group 1 in study HPV-048 with the proportions reported in the Safety Card subset in study HPV-008 (days 0-29) (Table 23).

Table 23: Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class within the 30-day (Days 0-29) post-vaccination period following each HPV vaccine dose by Age Strata (9-14 years and 15-25 years of age in study HPV-048) compared to those observed in studies HPV-013 (10-14 years of age) and study HPV-008 (15-25 years of age) (Total Vaccinated cohort – Group 1) [CBER generated]

	Study HPV-048 9-14 years N=82	Study HPV-013 10-14 years N=1035	Study HPV-048 15-25 years N=157	Study HPV-008* 15-25 years N=3184
Primary System Organ Class	n/%	n/%	n/%	n/%
At least one symptom	37 (45.1%)	386 (37.3%)	73 (46.5%)	1354 (42.5%)
At least one grade 3 symptom	4 (4.9%)		9 (5.7%)	
Blood and lymphatic system disorders	0 (0.0%)	3 (0.3%)	0 (0.0%)	9 (0.3%)
Cardiac disorders	0 (0.0%)	2 (0.2%)	0 (0.0%)	5 (0.2%)
Ear and labyrinth disorders	1 (1.2%)	10 (1.0%)	3 (1.9%)	15 (0.5%)
Endocrine disorders	0 (0.0%)	1 (0.1%)	1 (0.6%)	0 (0.0%)
Eye disorders	0 (0.0%)	0 (0.0%)	1 (0.6%)	31 (1.0%)
Gastrointestinal disorders	5 (6.1%)	28 (2.7%)	7 (4.5%)	154 (5.2%)
General disorders and administration site conditions	6 (7.3%)	51 (4.9%)	17 (10.8%)	244 (7.7%)
Hepatobiliary disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Immune system disorders	1 (1.2%)	5 (0.5%)	0 (0.0%)	10 (0.3%)
Infections and Infestations	17 (20.7%)	226 (21.8%)	28 (17.8%)	793 (24.9%)
Injury, poisoning and procedural complications	2 (2.4%)	21 (2.0%)	7 (4.5%)	44 (1.4%)
Investigations	0 (0.0%)	1 (0.1%)	0 (0.0%)	4 (0.1%)
Metabolism and nutrition disorders	1 (1.2%)	7 (0.7%)	1 (0.6%)	6 (0.2%)
Musculoskeletal and connective tissue disorders	5 (6.1%)	22 (1.3%)	10 (6.4%)	158 (5.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.2%)
Nervous system disorders	5 (6.1%)	54 (5.2%)	10 (6.4%)	321 (10.1%)
Psychiatric disorders	0 (0.0%)	2 (0.2%)	2 (1.3%)	30 (0.9%)
Renal and urinary disorders	0 (0.0%)	1 (0.1%)	0 (0.0%)	13 (0.4%)
Reproductive system and breast disorders	1 (1.2%)	23 (2.2%)	6 (3.8%)	144 (4.5%)
Respiratory, thoracic and mediastinal disorders	7 (8.5%)	67 (6.5%)	9 (5.7%)	160 (5.0%)
Skin and subcutaneous tissue disorders	1 (1.2%)	28 (2.7%)	7 (4.5%)	80 (2.5%)
Surgical and medical procedures	1 (1.2%)	5 (0.5%)	0 (0.0%)	9 (0.3%)
Vascular disorders	1 (1.2%)	4 (0.4%)	1 (0.6%)	13 (0.4%)

Study HPV-048: N= number of subjects with at least one documented dose within reaccod.xpt dataset
n= number of subjects presenting at least one type of symptom whatever the study vaccine administered
%=percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
Source: *Study HPV-008 – subjects in Diary Card subset from original application STN 125259/0 and STN 125259.0048; Study HPV-013 – subjects 10-14 years of age who received Cervarix formulation from original application STN 125259/0; STN 125259/132.1, Module 5.3.5.1.3, CSR HPV-048 reaccod.xpt dataset ; STN 125259/0, Module 5.3.1.5.3, CSR HPV-013, Supplement 23, p.121; STN 125259.0048, Module 5.3.5.1.3, CSR 008, Supplement 319, p. 10578

Reviewer's Comment: A higher proportion of musculoskeletal unsolicited adverse events in subjects 9-14 years of age in study HPV-048 (Group 1) as compared to subjects 10-14 years of age (study HPV-013). The wunsol.xpt datasets in study HPV-048 were reviewed for this System Organ Class (SOC) in this age group. The five Preferred Terms (PT) included torticollis (9 year old), osteochondrosis dissecans medial talus (trauma related, 11 year old), exacerbation of palindromic rheumatism (13 year old, recurrent, predated vaccination, resolved, not related; subject received dose 3 Cervarix without adverse events, no continuing meds), costochondritis and pain in extremity [foot] (2 14-year old subjects]. All these events

resolved, were not serious, and were assessed as unrelated to study material. Proportions of unsolicited were otherwise generally similar for different age strata and when subjects in study HPV-048 are compared to subjects in study HPV-013 (9-14 year old subjects compared to 10-14 year old subjects) or study HPV-008 (15-25 year old subjects in both studies).

New Onset Chronic Diseases (NOCDs) through active phase of follow-up period in Groups 1 and 2: Subjects with new onset chronic diseases in Group 1 and Group 2 are presented in Table 24.

Table 24: Study HPV-048 - Percentage of subjects reporting the occurrence of New Onset Chronic Diseases classified by MedDRA Primary System Organ Class and Preferred Term during active phase of the follow-up period (Total Vaccinated cohort-Groups 1 - 4)

		Group 2 N=240	Group 1 N=239	Group 3 N=241	Group 4
Primary System Organ Class	Preferred Term	n/%	n/%	n/%	n/%
At least one symptom		6/2.5%	[5/2.1%]3/1.3%	2/0.8%	4/1.7%
Endocrine disorders	Basedow's disease	0/0.0%	1/0.4%	0/0.0%	0/0.0%
	Hyperthyroidism	0/0.0%	0/0.0%	1/0.4%	0/0.0%
	Hypothyroidism	1/0.4%	0/0.0%	0/0.0%	1/0.4%
Immune system disorders	Food allergy	1/0.4%	0/0.0%	0/0.0%	0/0.0%
	Hypersensitivity	0/0.0%	0/0.0%	1/0.4%	1/0.4%
	Hypersensitivity, Drug	0/0.0%	0/0.0%	0/0.0%	2/0.8%
	Seasonal allergy	1/0.4%	[2/0.8%]1/0.4%	0/0.0%	0/0.0%
Metabolism and nutrition disorders	Diabetes mellitus	1/0.4%	0/0.0%	0/0.0%	0/0.0%
Respiratory, mediastinal and thoracic disorders	Asthma	0/0.0%	[2/0.8%] 1/0.4%	0/0.0%	0/0.0%
Skin and subcutaneous tissue disorders	Dermatitis, contact	2/0.8%	0/0.0%	0/0.0%	0/0.0%
	Urticaria	1/0.4%	0/0.0%	0/0.0%	0/0.0%

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n=number of subjects reporting at least once the symptom
%=percentage of subjects reporting at least once the symptom
Active phase = time from dose 1 through 1 month after last dose (usually 7 months in duration)
[bracketed number includes subjects located in wunsol.xpt and re-calculated percentage]
Source: STN 125259/106, CSR HPV-048, Table 47, p. 129

Reviewer's Comment: Few subjects in Group 1 (3/1.3%) or Group 2 (6/2.5%) developed NOCDs during participation in this trial. The proportions of subjects with NOCDs in pooled studies which supported initial licensure of Cervarix in females 10-14 years of age was 2.3% (N=1194) through Month 7 and 3.0% throughout the entire study period. The rates for 15-25 year old subjects were 1.1% (N=10946) through Month 7 and 2.6% through the entire study period. The rates overall in the active phase (through Month 7) were 1.7% (N=16142) and 2.4% through 4.3 years (mean follow-up 3 years). In Group 1, one subject 9 years of age was identified as having seasonal allergy at 108 days after vaccination which was mild in intensity, assessed as unrelated, and the subject recovered. Another 9-year old subject developed urticaria at 22 days after receipt of aluminum hydroxide, mild in intensity, assessed as unrelated to study material, and recovered. Other subjects with NOCD's ranged from 13 years to 23 years in Groups 1 and 2, age 17 years to 25 years in Groups 3 and 4. Accordingly, these data do not suggest an increased risk for NOCDs in 9 year olds following receipt of Cervarix.

New Onset Autoimmune Diseases (NOADs) through active phase of follow-up period in Groups 1-4 in Study HPV-048: The proportions of subjects with new onset autoimmune diseases during the active phase of the study in Group 1 (1/0.4%); Group 2 (2/0.8%); Group 3 (1/0.4%); and Group 4 (1/0.4%).

Reviewer's Comment: One case of Basedow's disease in Group 1 (15 year old), one case of hypothyroidism in Group 2 (23 year old), one case of diabetes mellitus in Group 2 (13 year old), one case of hypothyroidism in Group 4 (17 year old), and one case of hyperthyroidism in Group 3 (25 year old) were reported. None of these NOADs occurred in 9 year old subjects. The overall percentages of these events were comparable to the proportions reported in studies for both the Cervarix and the active control Havrix which supported initial licensure of Cervarix in 2009.

Medically Significant Adverse Events (MSAEs) during the active phase of follow-up period in Groups 1-4 in Study HPV-048: The proportions of subjects with MSAEs through the active phase of study HPV-048 (through one month after dose 3) were generally comparable across the four treatment groups [Group 1 (42/17.6%). Group 2 (45/18.8%), Group 3 (48/19.9%) and Group 4 (40 (16.7%)]. The most common MSAE (in >1% of subjects in any group) were headache, pharyngolaryngeal pain, procedural pain, viral infection, contusion, abdominal pain, back pain, pharyngitis, joint sprain, and depression.

Reviewer's Comment: MSAEs in study HPV-048 were reviewed in conjunction with those identified in the wunsol.xpt dataset for Group 1 (27 in the 9-17 year old age group and 15 in the 18-25 year old age group) and assessed by MedDRA System Organ Class and Preferred Term. For Group 1, the younger group had a higher proportion of medically significant adverse events, mostly attributable to a higher proportion of subjects with infections. In review of Group , a higher proportion of younger subjects experienced a medically significant adverse event, but these were distributed across several system organ classes, and no consistent pattern was identified among treatment groups. Overall, no clinically relevant specific medically significant adverse events were identified by these parameters.

Clinical Laboratory Evaluations, Study HPV-048: The numbers and percentages of subjects with laboratory results outside the normal ranges for hematology and biochemistry at Month 7 were low and observationally similar.

Reviewer's Comment: There were no appreciable clinically relevant abnormalities noted in laboratory results, and no appreciable consistent differences were noted between the 9-17 year old and 18-25 year old age groups.

Pregnancy Outcomes in all subjects (Groups 1-4. Study HPV-048): Ten pregnancies were recorded during the active phase of the study (up to Month 7), all in adult females ≥18 years of age. Overall, the outcomes were as follows: elective terminations of pregnancy in 4 subjects and 6 healthy infants (4 delivered by cesarean section and 2 by normal delivery).

Serious Adverse Events (SAEs) in study HPV-048: SAEs were reviewed from the datasets for all subjects. Narratives were reviewed for all subjects. Twenty-one subjects in total were identified from the wunsol.xpt dataset. In Groups 2 and 3, seven subjects experienced a SAE most proximal to receipt of aluminum hydroxide. No SAEs occurred in 9-year old subjects. All SAEs were ultimately assessed as unrelated to study material by the investigators. Please see Table A11 of Appendix 1 which includes all SAEs reported in all treatment groups.

Two SAEs were of interest by nature of event and/or by temporal relationship to receipt of Cervarix, although these were not apparently related to vaccination.

- **Subject ID 0102, Group 1:** 16 year old female received 2 doses of Cervarix (20μg HPV-16/20 μg HPV-18) on 10/26/07 and 11/28/07. She was diagnosed with **Grave's disease** on 12/11/07, 13 days after receipt of dose 2. Dose 3 was not administered. However, after review of lab test results from the day of dose 1, which were not available until after receipt of vaccine, the TSH was noted to be very low and the thyroid antibody levels were elevated. The investigator concluded that there was no reasonable possibility that the Graves' disease may have been caused by study vaccine and that it represented a pre-existing condition.
- **Subject ID 01546, Group 2:** 15 year old subject received Cervarix 20/20 on 11/3/07 and 5/27/08, and Al(OH)3 on 1/5/08. On 11/11/08, 6 months after dose 2 Cervarix, this subject developed a brainstem CVA and basilar artery thrombosis. The subject was hospitalized, received rehabilitation therapy for continued neurological deficits. The investigator indicated that the subject was started on the oral contraceptive Leios [0.02mg ethinyl estradiol & 0.1 mg levonorgestrel] contraceptive 11 days prior to event. The investigator assessed there was no reasonable possibility that the event was related to study vaccine.[9]

Reviewer's Comment: Based on the percentage of subjects with SAEs and the lack of any discernible pattern, this clinical reviewer concluded that no new safety signal is apparent in these data compared with the other pre-licensure data with regard to SAEs.

Adverse Events Leading to premature discontinuation of study vaccine and/or study in Groups 1-4, Study HPV-048: No AE or SAE assessed as related to study material led to premature discontinuation of study vaccine and/or study.

Concomitant medications in Study HPV-048, Groups 1 and 2: The most common medications used in that time period for both groups 1 and 2 included anti-pyretics (67/28.0% Group 1 and 54/22.5% Group 2) and any antibiotic (19/7.9% Group 1 and 12/5.0% Group 2). 84/34.9% of subjects in Group 3 and 95/39.6% of subjects in Group 4

[9] Christerson S and Stromberg B. Childhood stroke in Sweden I: Incidence, symptoms, risk factors and short-term outcome. Acta Paediatrica 2010; 99: 1641-1649. *In this retrospective review of medical records of 51 children [23 boys and 28 girls, median age 13 years] in Sweden who had experienced a stroke, the incidence of stroke was calculated to be 1.8 per 100,000 children. Risk factors included oral contraceptives, smoking and anemia. Of the 28 girls with stroke, six who used oral contraceptives experienced a stroke 7 days to 7 months after starting the oral contraceptive.*

took any concomitant medication. The most common medications Groups 3 and 4 were any anti-pyretics (57/23.7% and 64/26.7%, respectively) and any antibiotics (14/5.8% and 9/3.8%, respectively). (Source: STN 125259/106, CSR HPV-048, Table 50, p. 137, not shown here).

Reviewer's Comment: Fewer subjects overall took concomitant medication after Cervarix in study HPV-048 in the group that received the licensed formulation as compared to subjects 10-14 years of age in study HPV-013, in which 39.1% of HPV recipients took any concomitant medication.

Safety Conclusion: Based on the review of study HPV-048 and the safety database in pediatric females 9-17 years of age, the safety profile of Cervarix in females 9-25 years of age is comparable to the safety profile of Cervarix in females 10-25 years of age. No safety signal was identified in the pediatric age group or in the older age group, although the number of subjects in this particular study was small. Additional safety will be collected in the 9-year old age group in the post-marketing surveillance safety study which is ongoing. GSK provided a commitment to revise the post-marketing surveillance safety study to add 9-year old subjects to the study. In addition, results of two non-IND studies conducted in subjects 9-15 years of age will be submitted to provide additional safety data in subjects who receive Cervarix alone from clinical studies.

9 **Overview of Immunogenicity/Efficacy Across Trials:** Only one clinical study report (study HPV-048) contributed to assessment of immunogenicity/efficacy in females 9-14 years of age. Please see Immunogenicity results for study HPV-048.

10 **Overview of Safety:** One clinical study report (HPV-048) contributed to assessment of safety in females 9-25 years of age. Please see Safety Results for study HPV-048 for full discussion.

Post-marketing Exposure: The Post-Marketing Safety Update Report (PSUR 2009-2010) was reviewed by this reviewer as well as by the medical officer in the Office of Bioepidemiology (please see separate review by Dr. Michael Ngyuen). In the PSUR included in this supplement, PSUR, GSK indicated that the doses distributed were ----(b)(4)---- through 11/17/10. CBER requested that GSK provide available specific safety information pertaining to use of Cervarix in 9-year old subjects and subjects 9 through 17 years of age worldwide. GSK responded on 4/8/11 stating that up to the data lock point of the most recent PSUR dated 11/17/2010 GSK had received a total of 5,255 spontaneous case reports globally. About 58% of these were from subjects 9 through 17 years of age, and 13% of the cases were reported with an unspecified age. Only 6 spontaneous reports were from use of Cervarix in subjects 9 years of age, and the majority of those events were related to drug administration errors and injection site reactions. In subjects 9 through 17 years of age, the safety profile in general was comparable to the overall safety profile of the vaccine. The most frequently reported

MedDRA Preferred Terms per 100,000 doses distributed since launch of Cervarix for all age groups and for subjects 9 through 17 years are provided in Table 25.

Table 25: Reporting rate per 100,000 doses distributed Cervarix since product launch for the most frequently reported MedDRA Preferred Terms in all age groups and in subjects 9 through 17 years of age

MedDRA PTs	All age groups	MedDRA PTs	Ages 9 through 17 years
	Reporting rate per 100,000 doses distributed since launch		Reporting rate per 100,000 doses distributed since launch
Injection site pain	6.20	**Headache**	4.18
Pyrexia	5.33	**Injection site pain**	3.98
Headache	5.28	**Pyrexia**	3.65
Nausea	3.64	**Nausea**	2.71
Dizziness	3.32	**Dizziness**	2.58
Malaise	2.32	Malaise	1.56
Pain in extremity*	2.06	Pain in extremity*	1.36
Rash	1.78	**Syncope**	1.28
Vomiting	1.71	**Vomiting**	1.22
Myalgia	1.66	**Rash**	1.06
Syncope	1.51	**Abdominal pain**	1.04
Pain	1.45	Pallor	1.04
Fatigue	1.44	**Fatigue**	1.02
Injection site swelling	1.44	Pain	0.99
Drug exposure during pregnancy	1.42	**Myalgia**	0.93

Data Source: all spontaneous cases since launch in STN 125259/132.7, Module 1.11.2, Table 1, p. 1
*Description of individual cases were similar to pain at injection site or extended arm
Texts in bold were recognized events in the Safety Information for Cervarix

In summary, no safety signal was identified which would mandate that a separate general safety study be conducted.

11 Additional Clinical Issues

11.1 Directions for Use: There is no change in directions for use.

11.2 Dose Regimens and Administration: There is no change for dose regimens and administration.

11.3 Special Populations: With this application, the lower age indication will be lowered to include females as young as 9-years of age.

11.4 Pediatrics: With this application, females as young as 9-years of age will be added to the indicated population.

12 Conclusions – The immune responses to HPV-16 and HPV-18 elicited in 9-14 year old females are non-inferior to immune responses 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.

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 (9-14 years to subjects 10-14 years and 15-25 years) reviewed in studies which supported initial licensure of the product in 2009, as well as when pediatric subjects 9-17 year old age group are compared to adult females 18-25 year old age group. 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.

13 Recommendations

13.1 This reviewer recommends approval of this supplement, and lowering of lower age limit to include females as young as 9 years of age.

13.2 **Recommendation on Postmarketing Actions:** GSK provided a Risk Management Plan update and Postmarketing Safety Update Report (2009-2010). GSK has agreed to include nine year old subjects in the ongoing surveillance safety study in large health maintenance organizations. In addition, as noted in the Risk Management Plan provided to this BLA supplement (STN 125259/132.4 v.6 on 2/1/11) GSK has two ongoing non-IND coadministration studies in females as young as 9 years of age in foreign countries (study HPV-029 and HPV-030). In study HPV-029 (adminstration of Cervarix with or without Twinrix Pediatric in Denmark, Hungary, Sweden and Canada), 270 subjects 9-15 years of age will receive Cervarix at the licensed formulation according to the licensed dosing regimen). In study HPV-030 (administration of Cervarix with or without Engerix-B in Netherlands, Norway and Sweden), 247 subjects as young as 9 years of age will receive Cervarix at the licensed formulation according to the licensed dosing regimen). These studies will therefore provide additional safety data for use of Cervarix in females as young as 9 years of age. CBER has requested that GSK submit the results of these studies to the IND when they are completed.

13.3 **Labeling:** Appropriate changes were made to Package Insert regarding lowering the age indication to females as young as years of age. The upper age limit has not changed (25 years of age). In the package insert, safety data from the pediatric subjects 9-17years of age from Group 1 in study HPV-048 (n=82) and adult from females 18-25 years of age from Group 1 (n=157) were added to the totals within the safety tables for solicited and unsolicited adverse events. Inclusion of these additional subjects did not appreciably impact on overall rates of these adverse events. 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. In addition, the Patient Package Insert (PPI) was updated to include females 9 years of age.

14 **Comments and questions for the applicant:** CBER requested that 9-year old females be added to the post-marketing surveillance safety study in large health maintenance organizations. In addition, as specified in GSK's submitted Risk Management Plan, CBER requests that results of study HPV-029 (administration of Cervarix with or without Twinrix Pediatric) and study HPV-030 (administration of Cervarix with or without Engerix-B) be submitted to IND (b)(4) when results are available. All other responses were provided during the review of supplement 125259/132.