

BLA Pharmacovigilance Plan Review - Cervarix

Date: October 15, 2009
FDA STN: 125259
Sponsor: GlaxoSmithKline Biologicals (GSK)
Product: Cervarix™ Human Papillomavirus (HPV) Bivalent (Types 16 and 18)
Vaccine, Recombinant
Each 0.5mL dose contains:

20 mcg HPV 16 L1 protein
20 mcg HPV 18 L1 protein
500 mcg aluminum hydroxide
50 mcg 3-O-fesacyl-4'-monophosphoryl lipid A (MPL)
0.624 mg sodium dihydrogen phosphate dehydrate as buffer

Indication: Active immunization of girls and women aged 10 through 25 years for prevention of the following disease caused by the Human Papillomavirus (HPV) types 16 and 18 included in the vaccine (indication still under negotiation):

Cervical cancer

Cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma in situ

CIN grade 1

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1 BACKGROUND

1.1 Purpose, Scope and Objectives

This memo follows a request from the Office of Vaccine Research and Review (OVRR) for the Office of Biostatistics and Epidemiology (OBE) to review and comment on the safety data and pharmacovigilance plan for the Biologics License Application (BLA) for Cervarix®, sponsored by GSK.

Cervarix is a non-infectious, recombinant vaccine containing Virus-Like Particles (VLPs) of the L1 capsid proteins of human papillomavirus (HPV) types 16 and 18, with the

adjuvant AS04 consisting of aluminum hydroxide and monophosphoryl lipid A (MPL). If approved, it would be the first licensed vaccine in the United States (US) which contains MPL as an adjuvant. The proposed indication is for active immunization of girls and women aged 10–25 years for the prevention of the following diseases caused by infection with HPV types 16 and 18: cervical cancer and the precancerous lesions cervical intraepithelial neoplasia (CIN) grades 1, 2, and 3; and adenocarcinoma *in situ*. The proposed vaccination schedule consists of 3 doses, with the second and third doses occurring at 1 and 6 months, respectively.

Genital human papillomavirus (HPV) is the most common sexually transmitted disease in the US; an estimated 6 million people are infected each year. Although most infections are self-limited, persistent infection with types 16 and 18 are responsible for more than 70% of cervical cancers globally. Other oncogenic HPV types include 31, 33, 39, 45, 51, 52, 56, 58, and 59. Cervarix may provide cross-protection to some nonvaccine types. However, there is insufficient data to demonstrate this at the current time. Although cervical cancer rates and deaths have decreased in the US due to cervical cancer screening programs, an estimated 11,000 cases of invasive cervical cancer are diagnosed annually, with more than 4,000 deaths.

1.2 Regulatory History

An Investigational New Drug (IND) application for Cervarix was submitted in September 1998, followed by a BLA on March 29, 2007. In review of this original submission, CBER assessed that additional efficacy and safety data were required to complete the review. A *Complete Response* letter was sent to GSK on December 14, 2009 and a full response was made on March 27, 2009.

2 METHODS AND MATERIAL REVIEWED

2.1 Data and Information Sources

Clinical trial data :

Study Number	Size	Population
008 (pivotal)	18,648	Females aged 15–25 years, compared to Havrix
009	7,466	Females aged 15–25 years
013	2,067	Females aged 10–14 years, compared to Havrix

Endpoints : solicited and unsolicited adverse events 7 and 30 days after each vaccination; deaths; serious adverse events; study discontinuation due to adverse events; medically significant adverse events; new onset chronic and autoimmune diseases; and pregnancy exposures and outcomes.

- The pooled safety database of ~30,000 females aged 10–25 years (of whom ~16,000 subjects received ≥1 dose of Cervarix) was also reviewed.

Summary documents and secondary data analysis

- Vaccines & Related Biologic Products Advisory Committee (VRBPAC) brief and presentation slides by FDA
- VRBPAC brief and presentation slides by GSK
- Analysis on the risk of miscarriage using data from HPV-008 and HPV-009 studies performed by the National Cancer Institute (NCI)
- Periodic Safety Update Reports (PSUR) from the period of international launch in May 18, 2007 through May 17, 2009 from countries where Cervarix is already licensed were submitted by GSK

- Discussion Document on Observed Imbalance in Rates of Spontaneous Abortions Observed During the Perivaccination Period in Clinical Trials with Cervarix and associated tables and appendices, submitted by GSK
Study protocols
- GSK Phase IV concept protocol entitled, “Safety study of Cervarix in females aged 10–25 years in the US” and the supplementary “Cervarix Vaccine Pregnancy Registry Protocol”
Expert Opinion and Review Committees
- Input and comments were received from VRBPAC and the CBER Safety Working Group.

2.2 Analytic Methods and Assessment Criteria

Vaccine safety assessments were based on analyses of the all available preapproval and international postmarketing data, as described above. Additionally, experience gained from monitoring a prior US-licensed HPV vaccine (Gardasil®) was also used, principally to estimate the rates of vaccine uptake and rates of pregnancy exposure to determine the feasibility of the pharmacovigilance plans for Cervarix. The criteria used for safety signal determination and assessments of postmarketing plans were based on the FDA’s Guidance for Industry on *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*.

3 RESULTS OF REVIEW

3.1 Safety Concerns

- No significant differences were noted between the Cervarix and control groups for rates of deaths, serious adverse events, and events leading to study discontinuation.
- No safety concerns were identified with new onset autoimmune and chronic diseases . Given the low background rates and the biologically plausible relationship between disease onset and an enhanced immune response from adjuvanted vaccination, these events were of special interest. New onset adverse events of these types were reviewed by an expert panel of neurologists and rheumatologists, and no differences were observed between vaccine and control groups in the overall population or when examined by age group. While a statistically significant increased risk of autoimmune, musculoskeletal and inflammatory conditions was not identified in prelicensure data, detection of these rare adverse conditions is limited in clinical trials because of insufficient power to detect rare events.
- A safety signal was identified for spontaneous abortions . A higher rate of spontaneous abortions was noted in Cervarix recipients compared to Havrix (Hepatitis A) recipients among subjects whose pregnancies occurred around the time of vaccination (defined as last menstrual period (LMP) 30 days before until 45 days after vaccination) in the total vaccinated cohort (Tables 1 and 2). Additionally, the National Cancer Institute (NCI) identified higher rates of spontaneous abortion among 15–25 year olds who received the vaccine around the time of conception (0 to 90 days) in another secondary analysis. However, these observed rates are within the expected background rate for pregnancy loss, animal reproductive toxicology studies were negative, and there is no clear explanatory biologic mechanism.
- An NCI exploratory analysis examining data from HPV-008 and 009 (87.9% of all pregnancies), using a permutation test, identified a possible increased risk of spontaneous abortion <90 days postvaccination, where 15.4% of vaccine recipients and

9.6% of control subjects had miscarriages. Although the finding was not statistically significant (1-sided P-value of 0.036; critical value 0.025) and was limited by the use of a non-prespecified endpoint, NCI could not exclude an increased risk with vaccination within 90 days of LMP.

Table 1: Percentage of spontaneous abortions of completed pregnancies (total vaccinated cohort, data lock point August 31, 2008)

	HPV (n=392)	HAV 720 (n=316)	Alu (n=42)	HAV 360 (n=1)	Pooled Control (n=359)	Total (n=751)
Overall pregnancy outcomes	12.84%	11.78%	19.01%	0%	12.54%	12.69%
Pregnancy outcomes around the time of vaccination	13.78%	8.86%	16.67%	0%	9.75%	11.85%

Source: Table 34, page 38, FDA VRBPAC Brief

Table 2: Percentage of spontaneous abortions for completed pregnancy around the time of vaccination by age and treatment group

	Cervarix	Havrix	AI(OH) 3
Aged 15–25 years	13.37%	8.78%	8.33%
Aged >25 years	19.05%	--	19.35%

Source: FDA VRBPAC presentation

- PSUR data did not demonstrate any clear safety concerns : A review of all PSUR's containing data from over 90 countries in which Cervarix is currently licensed did not elucidate any clear safety signals. However, PSUR data are based on passive surveillance and must be interpreted with caution given the known limitations of passive surveillance systems such as reporting biases, incomplete data for medical review, and lack of sensitivity for adverse events with long latency periods.

- Concomitant vaccination was not analyzed .

3.2 Review of Proposed Pharmacovigilance Plan

- 2 Postmarketing Studies Currently Proposed : GSK initially proposed a study of 100,000 subjects in Scotland and a case control study to analyze general safety concerns, pregnancy outcomes, and autoimmune disease. Because this study was deemed unfeasible, CBER and GSK are in negotiations regarding a new concept protocol for (1) a safety study in a managed care organization and (2) a pregnancy registry:
- US Managed Care Organization (MCO) Safety Study : In a concept protocol, GSK has proposed a US-based phase IV, observational, cohort study in an MCO. A total of 50,000 females aged 10–25 years in the Cervarix group would be compared to 50,000 control subjects of the same age who were not exposed to Cervarix but who potentially received other age-appropriate vaccines. Propensity score matching methods would be used to address unequal distribution of risk factors. The primary objective would be to evaluate incidence of autoimmune disease (AID) within 12 months following first dose Cervarix vaccination, compared to unexposed cohort. A predefined list of AID's (page 8, concept protocol) would be evaluated using composite endpoints. A secondary objective will be to describe pregnancy outcomes, including spontaneous abortions, following administration of ≥ 1 dose of Cervarix relative to an equivalent time period in a

cohort that did not receive Cervarix. Preliminary power estimations indicate that a total of 162 pregnancies would need to be accrued in the Cervarix group and 324 in the control group to detect a relative risk of 2.0 with 80% power and assuming a spontaneous abortion rate of 8.7%. GSK states that the proposed study design should be sufficiently powered to rule out the relative risk (2.3) of spontaneous abortion observed in HPV-008.

- Coprimary endpoints for AID : (1) neuroinflammatory events that share the common pathophysiological mechanism of demyelination; and (2) all other AID's.
 - Secondary endpoints for AID : Autoimmune diseases would be analyzed in groups based on underlying immunologic mechanism of disease: (1) systemic diseases; (2) organ based T-cell mediated diseases; (3) organ based antibody mediated diseases; (4) psoriasis and fibromyalgia (separately assessed due to higher background rates).
- US Pregnancy Registry : The proposed GSK pregnancy registry would begin immediately following licensure to detect adverse pregnancy outcomes. Voluntary, passive reporting of eligible pregnancies would identify subjects for enrollment. Pregnancy outcomes of interest include birth defects, live births, still births, intrauterine fetal demise, spontaneous abortion and induced abortion. Patient recruitment would occur prospectively and depend on overall vaccine uptake. Solicitation of pregnancy outcome would occur at 3 and 6 months of the estimated date of delivery. Rates of pregnancy outcomes in prospectively reported pregnancies will be compared to those in other prospective population-based registries. Comparison rates would be derived from the CDC Metropolitan Atlanta Congenital Defects Program, the US National Birth Defects Prevention Network, and the CDC National Center for Health Statistics.
 - US pregnancy data would be augmented by 3 additional data sources :
- The ongoing pregnancy registry in the United Kingdom (UK) operated with UK's Health Protection Agency. Cervarix has been selected as the vaccine of choice in the national HPV vaccination program. Started in September 2008, the program intends to vaccinate girls aged 12–13 years (catch up vaccination for girls up to 18 years of age) over 3 years.
- The ongoing clinical trials HPV-040 (Finnish community trial), HPV-024 (the long term follow up study of HPV-001 and 007) and HPV-055 and 057 (cross-over vaccination of HPV-008). The Finnish study is a community-based randomized study using active (diary card of events around the time of vaccination) and passive surveillance of adverse events. The target population of 70,000 adolescents living among 33 different communities would be randomized 1:1:1 into 3 study arms: (a) 11 communities with 70% males and females vaccinated with Cervarix; (b) 11 communities with 70% of only females vaccinated with Cervarix; and (c) 11 communities with no vaccination.
- Electronic capture of pregnancy outcomes in the phase IV US based MCO safety study.

4 CONCLUSIONS

4.1 Safety Concerns

- Clinical trials and exploratory analyses conducted by NCI identified a potential increased risk of spontaneous abortions in Cervarix recipients, particularly if conception occurred within 0–90 days after vaccination. This safety concern is being addressed by a postmarketing requirement; further details can be found in the GSK PMR Notification Letter September 15, 2009 and in a PMR review memo.

- While a statistically significant increased risk of autoimmune, musculoskeletal and inflammatory conditions was not identified in prelicensure data, detection of these rare adverse conditions is limited in clinical trials. A postmarketing commitment to further refine the level of risk for these conditions is necessary.

4.2 Pharmacovigilance Plan

- OBE is currently in discussions with GSK on plans to conduct general safety surveillance, address the potential increased risk of spontaneous abortions, and further study autoimmune diseases following Cervarix administration.
- With respect to the MCO protocol concept, “reactive arthritis” should be included among the prespecified endpoints and implement SaTScan (spatial and temporal scan statistics) or similar statistical analysis.
- Also, FDA recommends that the MCO study achieve either 45,000 subjects who complete the 3-dose series, or accrue a total of at least 135,000 doses administered among all subjects to evaluate.

5 Current Status of the Postmarketing Protocols

Discussions with GSK regarding the postmarketing studies are ongoing. At this time, GSK has agreed to the following terms:

- **MCO Study on Autoimmune Diseases :** To conduct a US-based Phase IV, observational, cohort study in a managed care organization. The overall objective is to evaluate the incidence of new onset autoimmune disease 12 months after each vaccination among females 10 through 25 years of age. The study population will consist of at least 50,000 Cervarix recipients, compared to approximately 50,000 control subjects not vaccinated with Cervarix, but who potentially have received other recommended vaccines, including other HPV vaccines. At least 135,000 administered doses of Cervarix will be evaluated in this study. Annual interim reports will be submitted within 3 months after the yearly cut-off date. GSK has committed to the following study timeline: The final protocol will be submitted by March 2010. Depending on overall vaccine uptake, patient accrual will be completed by March 2013 and the study will be completed by September 2014. The final study report is projected to be submitted by March 2015, or 6 months after study completion.
- **Pregnancy Registry :** To conduct a prospective observational pregnancy exposure study that will actively collect data on Cervarix exposures occurring immediately before or during pregnancy, in addition to the associated pregnancy outcomes, and potential confounding factors, such as other medication exposures. The study will be initiated immediately after vaccine licensure and continue for at least 5 years. Annual interim reports will be submitted to FDA within 3 months after the yearly cut-off date.