Tab A

MERCK & CO., INC.
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9682300

GARDASIL®

[Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]

DESCRIPTION

GARDASIL* is a non-infectious recombinant, quadrivalent vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (amorphous aluminum hydroxyphosphate sulfate). The quadrivalent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

GARDASIL is a sterile preparation for intramuscular administration. Each 0.5-mL dose contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein.

Each 0.5-mL dose of the vaccine contains approximately 225 mcg of aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, and water for injection. The product does not contain a preservative or antibiotics.

After thorough agitation, GARDASIL is a white, cloudy liquid.

CLINICAL PHARMACOLOGY

Disease Burden

Human Papillomavirus (HPV) causes squamous cell cervical cancer (and its histologic precursor lesions Cervical Intraepithelial Neoplasia [CIN] 1 or low grade dysplasia and CIN 2/3 or moderate to high grade dysplasia) and cervical adenocarcinoma (and its precursor lesion adenocarcinoma *in situ* [AIS]). HPV also causes approximately 35-50% of vulvar and vaginal cancers. Vulvar Intraepithelial Neoplasia (VIN) Grade 2/3 and Vaginal Intraepithelial Neoplasia (VaIN) Grade 2/3 are immediate precursors to these cancers.

Cervical cancer prevention focuses on routine screening and early intervention. This strategy has reduced cervical cancer rates by approximately 75% in compliant individuals by monitoring and removing premalignant dysplastic lesions.

HPV also causes genital warts (condyloma acuminata) which are growths of the cervicovaginal, vulvar, and the external genitalia that rarely progress to cancer. HPV 6, 11, 16, and 18 are common HPV types.

HPV 16 and 18 cause approximately:

- 70% of cervical cancer, AIS, CIN 3, VIN 2/3, and VaIN 2/3 cases; and
- 50% of CIN 2 cases.

HPV 6, 11, 16, and 18 cause approximately:

- 35 to 50% of all CIN 1, VIN 1, and VaIN 1 cases; and
- 90% of genital wart cases.

Mechanism of Action

HPV only infects humans, but animal studies with analogous (animal, not human) papillomaviruses suggest that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses.

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CLINICAL STUDIES

CIN 2/3 and AIS are the immediate and necessary precursors of squamous cell carcinoma and adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent cancer; thus, they serve as surrogate markers for prevention of cervical cancer.

Efficacy was assessed in 4 placebo-controlled, double-blind, randomized Phase II and III clinical studies. The first Phase II study evaluated the HPV 16 component of GARDASIL (Protocol 005, N = 2391) and the second evaluated all components of GARDASIL (Protocol 007, N = 551). The Phase III studies, termed FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease), evaluated GARDASIL in 5442 (FUTURE I or Protocol 013) and 12,157 (FUTURE II or Protocol 015) subjects. Together, these four studies evaluated 20,541 women 16 to 26 years of age at enrollment. The median duration of follow-up was 4.0, 3.0, 2.4, and 2.0 years for Protocol 005, Protocol 007, FUTURE I, and FUTURE II, respectively. Subjects received vaccine or placebo on the day of enrollment, and 2 and 6 months thereafter. Efficacy was analyzed for each study individually and for all studies combined according to a prospective clinical plan.

Prophylactic Efficacy

GARDASIL is designed to prevent HPV 6-, 11-, 16-, and/or 18-related cervical cancer, cervical dysplasias, vulvar or vaginal dysplasias, or genital warts. GARDASIL was administered without prescreening for presence of HPV infection and the efficacy trials allowed enrollment of subjects regardless of baseline HPV status (i.e., Polymerase Chain Reaction [PCR] status or serostatus). Subjects who were infected with a particular vaccine HPV type (and who may already have had disease due to that infection) were not eligible for prophylactic efficacy evaluations for that type.

The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population, consisting of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative in cervicovaginal specimens and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7). Efficacy was measured starting after the Month 7 visit.

Overall, 73% of subjects were naïve (i.e., PCR negative and seronegative for all 4 vaccine HPV types) to all 4 vaccine HPV types at enrollment.

A total of 27% of subjects had evidence of prior exposure to or ongoing infection with at least 1 of the 4 vaccine HPV types. Among these subjects, 74% had evidence of prior exposure to or ongoing infection with only 1 of the 4 vaccine HPV types and were naïve (PCR negative and seronegative) to the remaining 3 types.

In subjects who were naïve (PCR negative and seronegative) to all 4 vaccine HPV types, CIN, genital warts, VIN, and VaIN caused by any of the 4 vaccine HPV types were counted as endpoints.

Among subjects who were positive (PCR positive and/or seropositive) for a vaccine HPV type at Day 1, endpoints related to that type were not included in the analyses of prophylactic efficacy. Endpoints related to the remaining types for which the subject was naïve (PCR negative and seronegative) were counted.

For example, in subjects who were HPV 18 positive (PCR positive and/or seropositive) at Day 1, lesions caused by HPV 18 were not counted in the prophylactic efficacy evaluations. Lesions caused by HPV 6, 11, and 16 were included in the prophylactic efficacy evaluations. The same approach was used for the other types.

GARDASIL was efficacious in reducing the incidence of CIN (any grade including CIN 2/3); AIS; genital warts; VIN (any grade); and VaIN (any grade) related to vaccine HPV types in those who were PCR negative and seronegative at baseline (Table 1).

Table 1
Analysis of Efficacy of GARDASIL in the PPE* Population**

Population	GARDASIL		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or 18-related CIN 2/3 or AIS					
Protocol 005***	755	0	750	12	100.0 (65.1, 100.0)
Protocol 007	231	0	230	1	100.0 (-3734.9, 100.0)
FUTURE I	2200	0	2222	19	100.0 (78.5, 100.0)
FUTURE II	5301	0	5258	21	100.0† (80.9, 100.0)
Combined Protocols‡	8487	0	8460	53	100.0† (92.9, 100.0)
HPV 6-, 11-, 16-, 18-related CIN (CIN 1, CIN 2/3) or AIS					
Protocol 007	235	0	233	3	100.0 (-137.8, 100.0)
FUTURE I	2240	0	2258	37	100.0† (89.5, 100.0)
FUTURE II	5383	4	5370	43	90.7 (74.4, 97.6)
Combined Protocols	7858	4	7861	83	95.2 (87.2, 98.7)
HPV 6-, 11-, 16-, or 18-related Genital Warts					
Protocol 007	235	0	233	3	100.0 (-139.5, 100.0)
FUTURE I	2261	0	2279	29	100.0 (86.4, 100.0)
FUTURE II	5401	1	5387	59	98.3 (90.2, 100.0)
Combined Protocols	7897	1	7899	91	98.9 (93.7, 100.0)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).
**See Table 2 for analysis of vaccine impact in the general population.
***Evaluated only the HPV 16 L1 VLP vaccine component of GARDASIL.
†P-values were computed for pre-specified primary hypothesis tests. All p-values were <0.001, supporting the following conclusions: efficacy against HPV 16/18-related CIN 2/3 is >0% (FUTURE II); efficacy against HPV 16/18-related CIN 2/3 is >25% (Combined Protocols); and efficacy against HPV 6/11/16/18-related CIN is >20% (FUTURE I).
‡Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.
n = Number of subjects with at least 1 follow-up visit after Month 7.
Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.
Note 2: The first analysis in the table (i.e., HPV 16- or 18-related CIN 2/3, AIS or worse) was the primary endpoint of the vaccine development plan.
Note 3: FUTURE I refers to Protocol 013; FUTURE II refers to Protocol 015.

GARDASIL was efficacious against HPV disease caused by each of the 4 vaccine HPV types.

In a pre-defined analysis, the efficacy of GARDASIL against HPV 16/18-related disease was 100% (95% CI: 87.9%, 100.0%) for CIN 3 or AIS and 100% (95% CI: 55.5%, 100.0%) for VIN 2/3 or VaIN 2/3. The efficacy of GARDASIL against HPV 6-, 11-, 16-, and 18-related VIN 1 or VaIN 1 was 100% (95% CI: 75.8%, 100.0%). These analyses were conducted in the PPE population that consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).

Efficacy in Subjects with Current or Prior Infection

GARDASIL is a prophylactic vaccine.

There was no clear evidence of protection from disease caused by HPV types for which subjects were PCR positive and/or seropositive at baseline.

Individuals who were already infected with 1 or more vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining vaccine HPV types.

General Population Impact

The general population of young American women includes women who are HPV-naïve (PCR negative and seronegative) and women who are HPV-non-naïve (PCR positive and/or seropositive), some of whom have HPV-related disease. The clinical trials population approximated the general population of American women with respect to prevalence of HPV infection and disease at enrollment. Analyses were conducted to evaluate the overall impact of GARDASIL with respect to HPV 6-, 11-, 16-, and 18-related cervical and genital disease in the general population. Here, analyses included events arising from HPV infections that were present at the start of vaccination as well as events that arose from infections that were acquired after the start of vaccination.

The impact of GARDASIL in the general population is shown in Table 2. Impact was measured starting 1 month Postdose 1. Prophylactic efficacy denotes the vaccine's efficacy in women who are naïve (PCR negative and seronegative) to the relevant HPV types at vaccination onset. General population impact denotes vaccine impact among women regardless of baseline PCR status and serostatus. The majority of CIN and genital warts, VIN, and VaIN detected in the group that received GARDASIL occurred as a consequence of HPV infection with the relevant HPV type that was already present at Day 1.

Table 2
General Population Impact for Vaccine HPV Types

Endpoints	Analysis	GARDASIL or HPV 16 L1 VLP Vaccine		Placebo		% Reduction (95% CI)
		N	Cases	N	Cases	
HPV 16- or 18-related CIN 2/3 or AIS	Prophylactic Efficacy*	9342	1	9400	81	98.8 (92.9, 100.0)
	HPV 16 and/or HPV 18 Positive at Day 1	--	121	--	120	--
	General Population Impact**	9831	122	9896	201	39.0 (23.3, 51.7)
HPV 16- or 18-related VIN 2/3 and VaIN 2/3	Prophylactic Efficacy*	8641	0	8667	24	100.0 (83.3, 100.0)
	HPV 16 and/or HPV 18 Positive at Day 1	--	8	--	2	
	General Population Impact**	8954	8	8962	26	69.1 (29.8, 87.9)
HPV 6-, 11-, 16-, 18-related CIN (CIN 1, CIN 2/3) or AIS	Prophylactic Efficacy*	8625	9	8673	143	93.7 (87.7, 97.2)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	--	161***	--	174***	--
	General Population Impact**	8814	170	8846	317	46.4 (35.2, 55.7)
HPV 6-, 11-, 16-, or 18-related Genital Warts	Prophylactic Efficacy*	8760	9	8786	136	93.4 (87.0, 97.0)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	--	49	--	48†	--
	General Population Impact**	8954	58	8962	184	68.5 (57.5, 77.0)

*Includes all subjects who received at least 1 vaccination and who were naïve (PCR negative and seronegative) to HPV 6, 11, 16, and/or 18 at Day 1. Case counting started at 1 Month Postdose 1.
**Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 Month Postdose 1.
***Includes 2 subjects (1 in each vaccination group) who underwent colposcopy for reasons other than an abnormal Pap and 1 placebo subject with missing serology/PCR data at day 1.
†Includes 1 subject with missing serology/PCR data at day 1.
Note 1: The 16- and 18-related CIN 2/3 or AIS composite endpoint included data from studies 005, 007, 013, and 015. All other endpoints only included data from studies 007, 013, and 015.
Note 2: Positive status at Day 1 denotes PCR positive and/or seropositive for the respective type at Day 1.
Note 3: Percent reduction includes the prophylactic efficacy of GARDASIL as well as the impact of GARDASIL on the course of infections present at the start of the vaccination.
Note 4: Table 2 does not include disease due to non-vaccine HPV types.

GARDASIL does not prevent infection with the HPV types not contained in the vaccine. Cases of disease due to non-vaccine types were observed among recipients of GARDASIL and placebo in Phase II and Phase III efficacy studies.

Among cases of CIN 2/3 or AIS caused by vaccine or non-vaccine HPV types in subjects in the general population who received GARDASIL, 79% occurred in subjects who had an abnormal Pap test at Day 1 and/or who were positive (PCR positive and/or seropositive) to HPV 6, 11, 16, and/or 18 at Day 1.

An interim analysis of the general population impact for GARDASIL was performed from studies 007, 013, and 015 that had a median duration of follow-up of 1.9 years. GARDASIL reduced the overall rate of CIN 2/3 or AIS caused by vaccine or non-vaccine HPV types by 12.2% (95% CI: -3.2%, 25.3%), compared with placebo.

An analysis of overall population impact for the HPV 16 L1 VLP vaccine was conducted from study 005 that had a median duration of follow-up of 3.9 years. The HPV 16 L1 VLP vaccine reduced the overall incidence of CIN 2/3 caused by vaccine or non-vaccine HPV types by 32.7% (95% CI: -34.7%, 67.3%) through a median duration of follow-up of 1.9 years (fixed case analysis) and by 45.3% (95% CI: 10.9%, 67.1%), through a median duration of follow-up of 3.9 years (end of study).

GARDASIL reduced the incidence of definitive therapy (e.g., loop electrosurgical excision procedure, laser conization, cold knife conization) by 16.5% (95% CI: 2.9%, 28.2%), and surgery to excise external

genital lesions by 26.5% (95% CI: 3.6%, 44.2%), compared with placebo for all HPV-related diseases. These analyses were performed in the general population of women which includes women regardless of baseline HPV PCR status or serostatus. GARDASIL has not been shown to protect against the diseases caused by all HPV types and will not treat existing disease caused by the HPV types contained in the vaccine. The overall efficacy of GARDASIL, described above, will depend on the baseline prevalence of HPV infection related to vaccine types in the population vaccinated and the incidence of HPV infection due to types not included in the vaccine.

Immunogenicity

Assays to Measure Immune Response

Because there were few disease cases in subjects naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical disease caused by HPV 6, 11, 16, and/or 18.

The immunogenicity of GARDASIL was assessed in 8915 women (GARDASIL N = 4666; placebo N = 4249) 18 to 26 years of age and female adolescents 9 to 17 years of age (GARDASIL N = 1471; placebo N = 583).

Type-specific competitive immunoassays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate.

Immune Response to GARDASIL

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of individuals who were seronegative and PCR negative to the relevant HPV type(s) at enrollment, remained HPV PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7), received all 3 vaccinations, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine.

Overall, 99.8%, 99.8%, 99.8%, and 99.5% of girls and women who received GARDASIL became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month Postdose 3 across all age groups tested. Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs peaked at Month 7. GMTs declined through Month 24 and then stabilized through Month 36 at levels above baseline (Table 3). The duration of immunity following a complete schedule of immunization with GARDASIL has not been established.

Table 3
Summary of Anti-HPV cLIA Geometric Mean Titers in the PPI* Population

Study Time	GARDASIL N** = 276		Aluminum-Containing Placebo N = 275	
	n***	Geometric Mean Titer (95% CI) mMU/mL†	n	Geometric Mean Titer (95% CI) mMU/mL
Anti-HPV 6				
Month 07	208	582.2 (527.2, 642.8)	198	4.6 (4.3, 4.8)
Month 24	192	93.7 (82.2, 106.9)	188	4.6 (4.3, 5.0)
Month 36	183	93.8 (81.0, 108.6)	184	5.1 (4.7, 5.6)
Anti-HPV 11				
Month 07	208	696.5 (617.8, 785.2)	198	4.1 (4.0, 4.2)
Month 24	190	97.1 (84.2, 112.0)	188	4.2 (4.0, 4.3)
Month 36	174	91.7 (78.3, 107.3)	180	4.4 (4.1, 4.7)
Anti-HPV 16				
Month 07	193	3889.0 (3318.7, 4557.4)	185	6.5 (6.2, 6.9)
Month 24	174	393.0 (335.7, 460.1)	175	6.8 (6.3, 7.4)
Month 36	176	507.3 (434.6, 592.0)	170	7.7 (6.8, 8.8)
Anti-HPV 18				
Month 07	219	801.2 (693.8, 925.4)	209	4.6 (4.3, 5.0)
Month 24	204	59.9 (49.7, 72.2)	199	4.6 (4.3, 5.0)
Month 36	196	59.7 (48.5, 73.5)	193	4.8 (4.4, 5.2)

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).
**Number of subjects randomized to the respective vaccination group who received at least 1 injection.
***Number of subjects in the per-protocol analysis with data at the specified study time point.
†mMU = milli-Merck units.
Note: These data are from Protocol 007.

Table 4 compares anti-HPV GMTs 1 month Postdose 3 among subjects who received Dose 2 between Month 1 and Month 3 and subjects who received Dose 3 between Month 4 and Month 8 (Table 4).

Table 4
Summary of GMTs for Variation of Dosing Regimen

Variation of Dosing Regimen	Anti-HPV 6		Anti-HPV 11		Anti-HPV 16		Anti-HPV 18	
	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)
Dose 2								
Early*	883	570.9 (542.2, 601.2)	888	824.6 (776.7, 875.5)	854	2625.3 (2415.1, 2853.9)	926	517.7 (482.9, 555.0)
On Time*	1767	552.3 (532.3, 573.1)	1785	739.7 (709.3, 771.5)	1737	2400.0 (2263.9, 2544.3)	1894	473.9 (451.8, 497.1)
Late*	313	447.4 (405.3, 493.8)	312	613.9 (550.8, 684.2)	285	1889.7 (1624.4, 2198.5)	334	388.5 (348.3, 433.3)
Dose 3								
Early**	495	493.1 (460.8, 527.8)	501	658.9 (609.5, 712.2)	487	2176.6 (1953.4, 2425.3)	521	423.4 (388.8, 461.2)
On Time**	2081	549.6 (531.1, 568.8)	2093	752.8 (723.8, 782.9)	2015	2415.0 (2286.3, 2550.9)	2214	486.0 (464.7, 508.2)
Late**	335	589.0 (537.0, 645.9)	339	865.3 (782.6, 956.7)	326	2765.9 (2408.7, 3176.2)	361	498.5 (446.2, 557.0)

*Early = 36 to 50 days Postdose 1; On-Time = 51 to 70 days Postdose 1; Late = 71 to 84 days Postdose 1.
**Early = 80 to 105 days Postdose 2; On-Time = 106 to 137 days Postdose 2; Late = 138 to 160 days Postdose 2.
Note: GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units.)

Bridging the Efficacy of GARDASIL from Young Adult Women to Adolescent Girls

A clinical study compared anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs in 10- to 15-year-old girls with responses in 16- to 23-year-old adolescent and young adult women. Among subjects who received GARDASIL, 99.1 to 100% became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive by 1 month Postdose 3.

Table 5 compares the 1 month Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs in 9- to 15-year-old girls with those in 16- to 26-year-old adolescent and young adult women.

Table 5
Immunogenicity Bridging Between 9- to 15-year-old Female Adolescents and 16- to 26-year-old Adult Women

Assay (cLIA)	9- to 15-year-old Female Adolescents (Protocols 016 and 018) N = 1121			16- to 26-year-old Adult Women (Protocols 013 and 015) N = 4229		
	n	GMT	(95% CI)	n	GMT	95% CI
Anti-HPV 6	927	931.3	(876.9, 989.2)	2827	542.4	(526.6, 558.7)
Anti-HPV 11	927	1305.7	(1226.2, 1390.4)	2827	766.1	(740.5, 792.6)
Anti-HPV 16	929	4944.9	(4583.5, 5334.8)	2707	2313.8	(2206.2, 2426.7)
Anti-HPV 18	932	1046.0	(971.2, 1126.5)	3040	460.7	(443.8, 478.3)

Note: GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units).

Anti-HPV responses 1 month Postdose 3 among 9- to 15-year-old girls were non-inferior to anti-HPV responses in 16- to 26-year-old adolescent and young adult women in the combined database of immunogenicity studies for GARDASIL.

On the basis of this immunogenicity bridging, the efficacy of GARDASIL in 9- to 15-year-old girls is inferred.

Studies with Other Vaccines

The safety and immunogenicity of co-administration of GARDASIL with hepatitis B vaccine (recombinant) (same visit, injections at separate sites) were evaluated in a randomized study of 1871 women aged 16 to 24 years at enrollment. Immune response to both hepatitis B vaccine (recombinant) and GARDASIL was non-inferior whether they were administered at the same visit or at a different visit.

INDICATIONS AND USAGE

GARDASIL is a vaccine indicated in girls and women 9-26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, and 18:

- Cervical cancer
- Genital warts (condyloma acuminata)

and the following precancerous or dysplastic lesions:

- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1

CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients of the vaccine.

Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL should not receive further doses of GARDASIL.

PRECAUTIONS

General

As for any vaccine, vaccination with GARDASIL may not result in protection in all vaccine recipients.

This vaccine is not intended to be used for treatment of active genital warts; cervical cancer; CIN, VIN, or VaIN.

This vaccine will not protect against diseases that are not caused by HPV.

GARDASIL has not been shown to protect against diseases due to non-vaccine HPV types.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. Low-grade fever itself and mild upper respiratory infection are not generally contraindications to vaccination.

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may have reduced antibody response to active immunization (see PRECAUTIONS, *Drug Interactions*).

As with other intramuscular injections, GARDASIL should not be given to individuals with bleeding disorders such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefits clearly outweigh the risk of administration. If the decision is made to administer GARDASIL to such persons, it should be given with steps to avoid the risk of hematoma following the injection.

Information for the Patient, Parent, or Guardian

The health care provider should inform the patient, parent, or guardian that vaccination does not substitute for routine cervical cancer screening. Women who receive GARDASIL should continue to undergo cervical cancer screening per standard of care.

The health care provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The health care provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see PRECAUTIONS and ADVERSE REACTIONS.

GARDASIL is not recommended for use in pregnant women.

The health care provider should inform the patient, parent, or guardian of the importance of completing the immunization series unless contraindicated.

Patients, parents, or guardians should be instructed to report any adverse reactions to their health care provider.

Drug Interactions

Use with Other Vaccines

Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with hepatitis B vaccine (recombinant) (see CLINICAL PHARMACOLOGY, *Studies with Other Vaccines*). Co-administration of GARDASIL with other vaccines has not been studied.

Use with Hormonal Contraceptives

In clinical studies, 13,293 subjects (vaccine = 6644; placebo = 6649) who had post-Month 7 follow-up used hormonal contraceptives for a total of 17,597 person-years (65.1% of the total follow-up time in the study for these subjects). Use of hormonal contraceptives or lack of use of hormonal contraceptives among study participants did not alter vaccine efficacy in the PPE population.

Use with Systemic Immunosuppressive Medications

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines (see PRECAUTIONS, *General*).

Carcinogenesis, Mutagenesis, Impairment of Fertility

GARDASIL has not been evaluated for the potential to cause carcinogenicity or genotoxicity.

GARDASIL administered to female rats at a dose of 120 mcg total protein, which corresponds to approximately 300-fold excess relative to the projected human dose, had no effects on mating performance, fertility, or embryonic/fetal survival.

Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in female rats at doses up to 300 times the human dose (on a mg/kg basis) and have revealed no evidence of impaired female fertility or harm to the fetus due to GARDASIL. However, it is not known whether GARDASIL can cause fetal harm when administered to a pregnant woman or if it can affect reproductive capacity. GARDASIL should be given to a pregnant woman only if clearly needed. An evaluation of the effect of GARDASIL on embryo-fetal, pre- and postweaning development was conducted using rats. One group of rats was administered GARDASIL twice prior to gestation, during the period of organogenesis (gestation day 6) and on lactation day 7. A second group of pregnant rats was administered GARDASIL during the period of organogenesis (gestation day 6) and on lactation day 7 only. GARDASIL was administered at 0.5 mL/rat/occasion (approximately 300-fold excess relative to the projected human dose on a mg/kg basis) by intramuscular injection. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-fetal or pre- and postweaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted in this study. In addition, there were no treatment-related effects on developmental signs, behavior, reproductive performance, or fertility of the offspring. The effect of GARDASIL on male fertility has not been studied.

In clinical studies, women underwent urine pregnancy testing prior to administration of each dose of GARDASIL. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL were instructed to defer completion of their vaccination regimen until resolution of the pregnancy.

During clinical trials, 2266 women (vaccine = 1115 vs. placebo = 1151) reported at least 1 pregnancy each. Overall, the proportions of pregnancies with an adverse outcome were comparable in subjects who received GARDASIL and subjects who received placebo. Overall, 40 and 41 subjects in the group that received GARDASIL or placebo, respectively (3.6% and 3.6% of all subjects who reported a pregnancy in the respective vaccination groups), experienced a serious adverse experience during pregnancy. The most common events reported were conditions that can result in Caesarean section (e.g., failure of labor, malpresentation, cephalopelvic disproportion), premature onset of labor (e.g., threatened abortions, premature rupture of membranes), and pregnancy-related medical problems (e.g., pre-eclampsia, hyperemesis). The proportions of pregnant subjects who experienced such events were comparable between the vaccination groups.

There were 15 cases of congenital anomaly in pregnancies that occurred in subjects who received GARDASIL and 16 cases of congenital anomaly in pregnancies that occurred in subjects who received placebo.

Further sub-analyses were conducted to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL or placebo. For pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received GARDASIL compared to 0 cases of congenital anomaly in the group that received placebo. The congenital anomalies seen in pregnancies with estimated onset within 30 days of vaccination included pyloric stenosis, congenital megacolon, congenital hydronephrosis, hip dysplasia and club foot. Conversely, in pregnancies with onset more than 30 days following vaccination, 10 cases of congenital anomaly were observed in the group that received GARDASIL compared with 16 cases of congenital anomaly in the group that received placebo. The types of anomalies observed were consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in women aged 16 to 26 years.

Pregnancy Registry for GARDASIL

Merck & Co., Inc. maintains a Pregnancy Registry to monitor fetal outcomes of pregnant women exposed to GARDASIL. Patients and health care providers are encouraged to report any exposure to GARDASIL during pregnancy by calling (800) 986-8999.

Lactation

It is not known whether vaccine antigens or antibodies induced by the vaccine are excreted in human milk.

Because many drugs are excreted in human milk, caution should be exercised when GARDASIL is administered to a nursing woman.

A total of 995 nursing mothers (vaccine = 500, placebo = 495) were given GARDASIL or placebo during the vaccination period of the clinical trials. GMTs in nursing and non-nursing mothers were as follows:

The GMTs in nursing mothers were 595.9 (95% CI: 522.5, 679.5) for anti-HPV 6, 864.3 (95% CI: 754.0, 990.8) for anti-HPV 11, 3056.9 (95% CI: 2594.4, 3601.8) for anti-HPV 16, and 527.2 (95% CI: 450.9, 616.5) for anti-HPV 18. The GMTs for women who did not nurse during vaccine administration were 540.1 (95% CI: 523.5, 557.2) for anti-HPV 6, 746.3 (95% CI: 720.4, 773.3) for anti-HPV 11, 2290.8 (95% CI: 2180.7, 2406.3) for anti-HPV 16, and 456.0 (95% CI: 438.4, 474.3) for anti-HPV 18.

Overall, 17 and 9 infants of subjects who received GARDASIL or placebo, respectively (representing 3.4% and 1.8% of the total number of subjects who were breast-feeding during the period in which they received GARDASIL or placebo, respectively), experienced a serious adverse experience. None was judged by the investigator to be vaccine related.

In clinical studies, a higher number of breast-feeding infants (n = 6) whose mothers received GARDASIL had acute respiratory illnesses within 30 days post-vaccination of the mother as compared to infants (n = 2) whose mothers received placebo. In these studies, the rates of other adverse experiences in the mother and the nursing infant were comparable between vaccination groups.

Pediatric Use

The safety and efficacy of GARDASIL have not been evaluated in children younger than 9 years.

Geriatric Use

The safety and efficacy of GARDASIL have not been evaluated in adults above the age of 26 years.

ADVERSE REACTIONS

In 5 clinical trials (4 placebo-controlled), subjects were administered GARDASIL or placebo on the day of enrollment, and approximately 2 and 6 months thereafter. Few subjects (0.1%) discontinued due to adverse experiences. In all except 1 of the clinical trials, safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL or placebo. The subjects who were monitored using VRC-aided surveillance included 5088 girls and women 9 through 26 years of age at enrollment who received GARDASIL and 3790 girls and women who received placebo.

Common Adverse Experiences

Vaccine-related Common Adverse Experiences

The vaccine-related adverse experiences that were observed among female recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients are shown in Table 6.

Table 6
Vaccine-related Injection-site and Systemic Adverse Experiences*

Adverse Experience (1 to 5 Days Postvaccination)	GARDASIL (N = 5088) %	Aluminum-Containing Placebo (N = 3470) %	Saline Placebo (N = 320) %
Injection Site			
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.6	18.4	12.1
Pruritus	3.1	2.8	0.6

Adverse Experience (1 to 15 Days Postvaccination)	GARDASIL (N = 5088) %	Placebo (N = 3790) %
Systemic		
Fever	10.3	8.6

*The vaccine-related adverse experiences that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.

All-cause Common Systemic Adverse Experiences

All-cause systemic adverse experiences for female subjects that were observed at a frequency of greater than or equal to 1% where the incidence in the vaccine group was greater than or equal to the incidence in the placebo group are shown in Table 7.

Table 7
All-cause Common Systemic Adverse Experiences

Adverse Experience (1 to 15 Days Postvaccination)	**GARDASIL** (N = 5088) %	**Placebo** (N = 3790) %
Pyrexia	13.0	11.2
Nausea	6.7	6.6
Nasopharyngitis	6.4	6.4
Dizziness	4.0	3.7
Diarrhea	3.6	3.5
Vomiting	2.4	1.9
Myalgia	2.0	2.0
Cough	2.0	1.5
Toothache	1.5	1.4
Upper respiratory tract infection	1.5	1.5
Malaise	1.4	1.2
Arthralgia	1.2	0.9
Insomnia	1.2	0.9
Nasal congestion	1.1	0.9

Evaluation of Injection-site Adverse Experiences by Dose

An analysis of injection-site adverse experiences in female subjects by dose is shown in Table 8. Overall, 94.3% of subjects who received GARDASIL judged their injection-site adverse experience to be mild or moderate in intensity.

Table 8
Postdose Evaluation of Injection-site Adverse Experiences

	Vaccine (% occurrence)				Aluminum-Containing Placebo (% occurrence)				Saline Placebo (% occurrence)			
Adverse Experience	Post-dose 1	Post-dose 2	Post-dose 3	Post Any Dose	Post-dose 1	Post-dose 2	Post-dose 3	Post Any Dose	Post-dose 1	Post-dose 2	Post-dose 3	Post Any Dose
Pain	63.4	60.7	62.7	83.9	57.0	47.8	49.5	75.4	33.7	20.3	27.3	48.6
Mild/Moderate	62.5	59.7	61.2	81.1	56.6	47.3	48.9	74.1	33.3	20.3	27.0	48.0
Severe	0.9	1.0	1.5	2.8	0.4	0.5	0.6	1.3	0.3	0.0	0.3	0.6
Swelling*	10.2	12.8	15.1	25.4	8.2	7.5	7.6	15.8	4.4	3.0	3.3	7.3
Mild/Moderate	9.6	11.9	14.3	23.3	8.0	7.2	7.3	15.2	4.4	3.0	3.3	7.3
Severe	0.6	0.8	0.8	2.0	0.2	0.3	0.2	0.6	0.0	0.0	0.0	0.0
Erythema*	9.2	12.1	14.7	24.7	9.8	8.4	8.9	18.4	7.3	5.3	5.7	12.1
Mild/Moderate	9.0	11.7	14.3	23.7	9.5	8.3	8.8	18.0	7.3	5.3	5.7	12.1
Severe	0.2	0.3	0.4	0.9	0.3	0.1	0.1	0.4	0.0	0.0	0.0	0.0

*Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

Evaluation of Fever by Dose

An analysis of fever in girls and women by dose is shown in Table 9.

Table 9
Postdose Evaluation of Fever

	Vaccine (% occurrence)			Placebo (% occurrence)		
Temperature (°F)	Postdose 1	Postdose 2	Postdose 3	Postdose 1	Postdose 2	Postdose 3
≥100 to <102	3.7	4.1	4.4	3.1	3.8	3.6
≥102	0.3	0.5	0.5	0.3	0.4	0.6

Serious Adverse Experiences

A total of 102 subjects out of 21,464 total subjects (9- to 26-year-old girls and women and 9- to 15-year-old boys) who received both GARDASIL and placebo reported a serious adverse experience on Day 1-15 following any vaccination visit during the clinical trials for GARDASIL. The most frequently reported serious adverse experiences for GARDASIL compared to placebo and regardless of causality were:

headache	(0.03% GARDASIL vs. 0.02% Placebo),
gastroenteritis	(0.03% GARDASIL vs. 0.01% Placebo),
appendicitis	(0.02% GARDASIL vs. 0.01% Placebo),
pelvic inflammatory disease	(0.02% GARDASIL vs. 0.01% Placebo).

One case of bronchospasm and 2 cases of asthma were reported as serious adverse experiences that occurred during Day 1-15 of any vaccination visit.

Deaths

Across the clinical studies, 17 deaths were reported in 21,464 male and female subjects. The events reported were consistent with events expected in healthy adolescent and adult populations. The most common cause of death was motor vehicle accident (4 subjects who received GARDASIL and 3 placebo subjects), followed by overdose/suicide (1 subject who received GARDASIL and 2 subjects who received placebo), and pulmonary embolus/deep vein thrombosis (1 subject who received GARDASIL and 1 placebo subject). In addition, there were 2 cases of sepsis, 1 case of pancreatic cancer, and 1 case of arrhythmia in the group that received GARDASIL, and 1 case of asphyxia in the placebo group.

Systemic Autoimmune Disorders

In the clinical studies, subjects were evaluated for new medical conditions that occurred over the course of up to 4 years of follow up. The number of subjects who received both GARDASIL and placebo and developed a new medical condition potentially indicative of a systemic immune disorder is shown in Table 10.

Table 10
Summary of Subjects Who Reported an Incident Condition Potentially Indicative of Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL

Potential Autoimmune Disorder	GARDASIL (N = 11,813)	Placebo (N = 9701)
Specific Terms	**3 (0.025%)**	**1 (0.010%)**
Juvenile arthritis	1	0
Rheumatoid arthritis	2	0
Systemic lupus erythematosus	0	1
Other Terms	**6 (0.051%)**	**2 (0.021%)**
Arthritis	5	2
Reactive Arthritis	1	0
N = Number of subjects enrolled		

Safety in Concomitant Use with Other Vaccines

The safety of GARDASIL when administered concomitantly with hepatitis B vaccine (recombinant) was evaluated in a placebo-controlled study. There were no statistically significant higher rates in systemic or injection-site adverse experiences among subjects who received concomitant vaccination compared with those who received GARDASIL or hepatitis B vaccine alone.

Reporting of Adverse Events

The US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967 or report on line to www.vaers.hhs.gov.

DOSAGE AND ADMINISTRATION

Dosage

GARDASIL should be administered intramuscularly as 3 separate 0.5-mL doses according to the following schedule:

First dose: at elected date
Second dose: 2 months after the first dose
Third dose: 6 months after the first dose

Method of Administration

GARDASIL should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

GARDASIL must not be injected intravascularly. Subcutaneous and intradermal administration have not been studied, and therefore are not recommended.

The prefilled syringe is for single use only and should not be used for more than 1 individual. For single-use vials a separate sterile syringe and needle must be used for each individual.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine.

After thorough agitation, GARDASIL is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the product if particulates are present or if it appears discolored.

Single-dose Vial Use

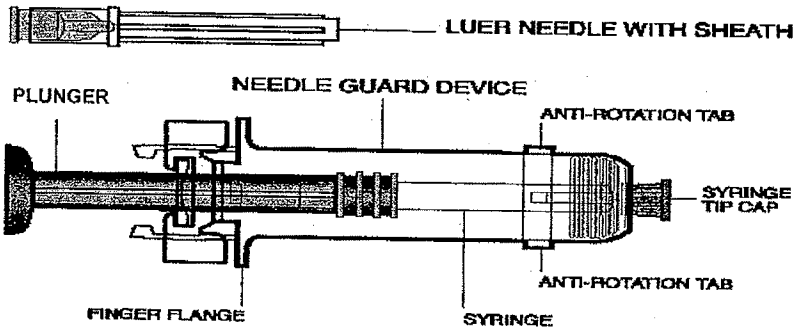
Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

Prefilled Syringe Use

Inject the entire contents of the syringe.

GARDASIL®
[Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] 9682300

Instructions for using the prefilled single-dose syringes preassembled with needle guard (safety) device



NOTE: Please use the enclosed needle for administration. If a different needle is chosen, it should fit securely on the syringe and be no longer than 1 inch to ensure proper functioning of the needle guard device. Two detachable labels are provided which can be removed after the needle is guarded.

Remove Syringe Tip Cap. Attach Luer Needle. Depress both Anti-Rotation Tabs to secure syringe and attach Luer Needle by twisting in clockwise direction. **Remove Needle Sheath. Administer injection** per standard protocol as stated above under DOSAGE AND ADMINISTRATION. Depress the Plunger while grasping the Finger Flange **until the entire dose has been given.** The Needle Guard Device will **NOT** activate to cover and protect the needle unless the **ENTIRE** dose has been given. Remove needle from the vaccine recipient. Release the Plunger and allow syringe to move up until the entire needle is guarded. For documentation of vaccination, remove detachable labels by pulling slowly on them. **Dispose in approved sharps container.**

HOW SUPPLIED

Vials

No. 4045 — GARDASIL is supplied as a carton of one 0.5-mL single-dose vial, **NDC** 0006-4045-00.

No. 4045 — GARDASIL is supplied as a carton of ten 0.5-mL single-dose vials, **NDC** 0006-4045-41.

Syringes

No. 4109 — GARDASIL is supplied as a carton of one 0.5-mL single-dose prefilled Luer Lock syringe, preassembled with UltraSafe Passive®† delivery system. A one-inch, 25-gauge needle is provided separately in the package. **NDC** 0006-4109-31.

No. 4109 — GARDASIL is supplied as a carton of six 0.5-mL single-dose prefilled Luer Lock syringes, preassembled with UltraSafe Passive® delivery system. One-inch, 25-gauge needles are provided separately in the package. **NDC** 0006-4109-06.

Storage

Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.

Manuf. and Dist. by:
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued June 2006

† UltraSafe Passive® delivery system is a Trademark of Safety Syringes, Inc.

Tab B

VAERS Line List Report

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 292052-1

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
21.0	F	Unknown	Unknown		20-Sep-2007	12-Mar-2008	AZ	WAES0708USA01192	12-Mar-2008

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL	0	Unknown	Intramuscular	

Seriousness: NO CONDITIONS, NOT SERIOUS

MedDRA PT Anogenital warts, Cryotherapy, Vaccine positive rechallenge

Symptom Text: Information has been received from a physician concerning an approximately 21 year old female who in June 2007, was vaccinated IM with Gardasil. Concomitant therapy included hormonal contraceptives (unspecified). Two days after receiving the first dose of Gardasil, the patient developed groin warts. There is no known history of these warts. The patient came back in about a month later and was given the second dose of Gardasil. A few days after receiving the second dose, the patient had a huge outbreak of warts. The patient was treated with cryotherapy. The patient did not notify the physician of the warts until the second outbreak occurred. Medical attention was sought. The patient's outcome was not reported. Additional information has been requested.

Other Meds: hormonal contraceptives

Lab Data: Unknown

History: Unknown

Prex Illness:

Prex Vax Illns:

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 301339-1

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
17.0	F	28-Sep-2007	15-Oct-2007	17	18-Dec-2007	18-Jan-2008	--	WAES0712USA00198	18-Jan-2008

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL	0	Unknown	Unknown	

Seriousness: ER VISIT, NOT SERIOUS

MedDRA PT Anogenital warts, Pyrexia

Symptom Text: Information has bee received from a consumer concerning her 17 year old daughter with no medical history and an allergy to sulfa, who on 28-SEP-2007 was vaccinated with a first dose of Gardasil. Concomitant therapy included hormonal contraceptives (unspecified) and homeopathic medications (unspecified). Prior to being vaccinated with Gardasil the patient was tested for HPV and genital warts and all her test came back negative. On 15-OCT-2007 (also reported as 19-OCT-2007) the patient experienced a fever, and broke out with white bumps that were diagnosed as genital warts. The patient was treated with an unspecified medication. Approximately one week later the patients genital warts had completely went away. The patient was seen by the physician. A blood test for HIgG and IgM were performed (no results provided). The patient recovered on an unspecified date. Additional information is not expected.

Other Meds: Homeopathic medications, hormonal contraceptives

Lab Data: Diagnostic laboratory - blood test for HIgG and IgM

History:

Prex Illness: Sulfonamide allergy

Prex Vax Illns:

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 300862-1

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
16.0	F	Unknown	Unknown		18-Dec-2007	17-Jan-2008	--	WAES0711USA03916	17-Jan-2008

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL		Unknown	Unknown	

Seriousness: ER VISIT, NOT SERIOUS

MedDRA PT Skin papilloma

Symptom Text: Information has been received from a licensed practical nurse concerning a 16 year old female who on an unspecified date was vaccinated with Gardasil (lot # unknown) injection. Subsequently, on an unspecified date the patient developed warts on hands after receiving Gardasil. Medical attention was sought. The patient's warts on hands persisted. The patient had received 2 doses of Gardasil. No further information was provided. Additional information has been requested.

Other Meds: Unknown

Lab Data: Unknown

History: Unknown

Prex Illness:

Prex Vax Illns:

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 288998-1

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
18.0	F	30-May-2007	04-Jul-2007	35	26-Aug-2007	31-Aug-2007	OK		31-Aug-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL	1	Unknown	Unknown	

Seriousness: NO CONDITIONS, NOT SERIOUS

MedDRA PT Skin papilloma

Symptom Text: My daughter began to have facial(flat) warts on her face and chest after the 2nd dose of Gardasil. There are many warts on her face and chest at least 20 or more. She has never had this problem before receiving the vaccine. She was treated for warts by her Doctor and now has been referred to Dermatology. She has not recovered yet. She will not receive the 3rd dose.

Other Meds: none

Lab Data:

History: none

Prex Illness: no

Prex Vax Illns:

VAERS Line List Report

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 262735-2 (S) **Related reports:** 262735-1; 262735-3; 262735-4

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
16.0	F	31-Jul-2006	13-Aug-2006	13	15-Dec-2006	29-Dec-2006	MS	200602493	29-Dec-2006

VAX Detail:

Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
MNQ	AVENTIS PASTEUR	42107A		Unknown	Intramuscular	
HPV4	MERCK & CO. INC.	0697F		Unknown	Intramuscular	

Seriousness: HOSPITALIZED, SERIOUS

MedDRA PT Asthenia, Guillain-Barre syndrome, Hypoaesthesia

Symptom Text: Initial report received on 22/Sep/2006 from the Centers for Disease Control and Prevention (CDC). A 16 year old female patient had received an intramuscular, first dose injection of Menactra, lot number reported as 42017AA; and an intramuscular, first dose injection of Human Papillomavirus Recombinant Vaccine, lot number 0697F; on 31/Jul/2006. On or around 13/Aug/2006, the patient experienced numbness and tingling in her feet and hands. The symptoms persisted and had slightly worsened at the time of her examination by a physician on 21/Aug/2006. At that time, "neurological examination was normal." She had and elevated sedimentation rate (39), mild proteinuria, and "otherwise normal labs." Other laboratory tests performed, (specific results not provided), included a blood count, blood chemistries, pregnancy test and drug screen. MRI was performed of the brain, cervical, thoracic and lumbosacral spine. MRI of the lumbosacral spine showed a (possibly old, chronic) subarachnoid cyst. The patient was referred to and examined by a neurologist on 25/Aug/2006. During that exam, she was found to have weakened severely. She was admitted to a pediatric intensive care unit for suspected Guillain Barre syndrome which was confirmed by lumbar puncture. Lumbar puncture results were not provided. She was treated with IVIG with rapid improvement; and after five days of hospitalization, was discharged to home. Per the reported, she is slowly improving and had residual weakness. Recovery status was documented as unknown. As per the CDC this case was confirmed by CISA (Clinical Immunization Safety Assessment network) as being Guillain Barre syndrome following Menactra vaccination. Follow-up information received 27/Sep/2006 from the Centers for Disease Control and Prevention. Per the reported, the patient was hospitalized on 25/Aug/2006. The date of discharge was not reported. The patient's Guillain Barre Syndrome was confirmed by lumbar puncture testing.

Other Meds:

Lab Data:

History:

Prex Illness:

Prex Vax Illns:

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 306241-1

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
17.0	F	19-Feb-2008	19-Feb-2008	0	03-Mar-2008	04-Mar-2008	CA	WAES0802USA05226	04-Mar-2008

VAX Detail:

Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
MNQ	SANOFI PASTEUR	NULL		Unknown	Unknown	
HPV4	MERCK & CO. INC.	NULL	0	Unknown	Unknown	
DTAP	UNKNOWN MANUFACTURER	NULL		Unknown	Unknown	

Seriousness: ER VISIT, NOT SERIOUS

MedDRA PT Convulsion, Face injury, Fall, Gingival injury, Head injury, Laceration, Syncope

Symptom Text: Information has been received from a physician concerning a 17 year old female with no medical history and no drug allergies, who on 19-FEB-2008 was vaccinated with a 0.5mL dose of Gardasil. Concomitant vaccinations included MENACTRA and DTaP. On 19-FEB-2008 the patient fainted, fell off the table, hit her head on the ground, and had a seizure. The patient also had a cut on the bridge of her nose and gums. The patient went to the emergency room and was released the same day. The physician thought the seizure was due to the head trauma. The patient recovered on an unspecified date. No product quality complaint was involved. Upon internal review seizure was considered to be an other important medical event. Additional information has been requested.

Other Meds:

Lab Data: Unknown

History: None

Prex Illness:

Prex Vax Illns:

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 290582-1

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
17.0	F	31-Jul-2007	31-Jul-2007	0	14-Sep-2007	17-Sep-2007	FR	WAES0709USA01406	17-Sep-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL		Unknown	Intramuscular	

Seriousness: NO CONDITIONS, NOT SERIOUS

MedDRA PT Abortion spontaneous, Drug exposure during pregnancy

Symptom Text: Information has been received from a healthcare professional, concerning a 17 year old female patient who was unknowingly pregnant when vaccinated on 31-JUL-2007 with the first dose of Gardasil (lot # not provided). On 03-AUG-2007, it was determined that she was pregnant. On 14-AUG-2007 she had a spontaneous abortion. She completely recovered (date, duration and details not provided). The event of spontaneous abortion was considered to be serious as an other important medical event. This file is closed. Other business partner numbers included: E2007-05931.

Other Meds: Unknown

Lab Data: Unknown

History:

Prex Illness: Pregnancy NOS (LMP = Unknown)

Prex Vax Illns:

Vaers Id: 277166-1 (S) **Related reports:** 277166-2

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
26.0	F	27-Mar-2007	27-Mar-2007	0	23-Apr-2007	24-Apr-2007	--	WAES0704USA02270	25-Apr-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL	1	Unknown	Unknown	

Seriousness: ER VISIT, HOSPITALIZED, LIFE THREATENING, PERMANENT DISABILITY, SERIOUS

MedDRA PT Abortion spontaneous, Drug exposure during pregnancy, Pregnancy test positive, Uterine dilation and curettage, Vaginal haemorrhage, Vaginitis bacterial

Symptom Text: Information has been received from a physician for the Pregnancy registry for GARDASIL, concerning a 26 year old female patient with a history of first trimester miscarriage in 2006 who on 25-JAN-2007 was vaccinated IM with a first dose of HPV. The physician reported that on 27-MAR-2007 the patient was vaccinated with second dose of HPV and had a positive pregnancy test the next day. The patient presented to the physician's office on 09-APR-2007 with vaginal bleeding and a pelvic ultrasound determined that she was suffering a spontaneous abortion. She was at 6 weeks gestation. The patient was admitted to the hospital on the night of 09-APR-2007 with severe vaginal hemorrhaging and underwent an emergency dilation and curettage procedure. The patient was recovering without complication. The physician added that, on 27-MAR-2007, the patient was diagnosed with bacterial vaginosis but she did not take the prescribed treatment. The physician considered spontaneous abortion to be significantly disabling and life threatening. Additional information has been requested.

Other Meds: Unknown

Lab Data: pelvic ultrasound 04/09/07 spontaneous abortion; complete blood cell Result not reported; total serum human 03/28/07 positive

History: Miscarriage

Prex Illness:

Prex Vax Illns:

Vaers Id: 277814-1

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
16.0	F	16-Apr-2007	17-Apr-2007	1	03-May-2007	04-May-2007	AZ	WAES0704USA05024	04-May-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL		Unknown	Unknown	

Seriousness: NO CONDITIONS, NOT SERIOUS

MedDRA PT Guillain-Barre syndrome, Hypoaesthesia, Muscular weakness

Symptom Text: Information has been received from a physician concerning a 16 year old female (also reported as 18 year old) who on 16-APR-2007 was vaccinated with a dose of Gardasil. Since 1 day post-injection, the patient had progressive bilateral leg numbness and weakness and motor weakness. The physician inquired about the possibility of Guillian Barre Syndrome. At the time of this report, the outcome was unknown. Upon internal review, progressive bilateral leg numbness and weakness and motor weakness were considered to be other important medical events. No further information is available.

Other Meds: Unknown

Lab Data: Unknown

History: Unknown

Prex Illness:

Prex Vax Illns:

Vaers Id: 296713-1 (S)

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
19.0	F	Unknown	Unknown		12-Oct-2007	28-Nov-2007	--	WAES0709USA01029	29-Nov-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL	0	Unknown	Intramuscular	

Seriousness: ER VISIT, HOSPITALIZED, LIFE THREATENING, PERMANENT DISABILITY, SERIOUS

MedDRA PT Guillain-Barre syndrome

Symptom Text: Information has been received from a nurse practitioner concerning an approximately 19 year old female who was vaccinated IM with a first dose of Gardasil. Subsequently, the patient was diagnosed with Guillain-barre syndrome and was hospitalized. The patient's Guillain-Barre syndrome persisted. No product quality complaint was involved. Guillain-barre syndrome was considered to be disabling and immediately life-threatening. Additional information has been requested.

Other Meds: Unknown

Lab Data: Unknown

History: Unknown

Prex Illness:

Prex Vax Illns:

Vaers Id: 268143-1 (S) **Related reports:** 268143-2; 268143-3; 268143-4

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
13.0	F	22-Nov-2006	30-Nov-2006	8	03-Dec-2006	04-Dec-2006	AK		22-Feb-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL	0	Unknown	Intramuscular	PPV

Seriousness: ER VISIT, HOSPITALIZED, LIFE THREATENING, SERIOUS

MedDRA PT Autonomic nervous system imbalance, Back pain, Extubation, Fall, Gait disturbance, Guillain-Barre syndrome, Hypertension, Hypoaesthesia, Hyporeflexia, Intubation, Muscular weakness, Neuralgia, Pneumonia haemophilus, Respiratory failure, Staphylococcal infection, Tachycardia, Tracheostomy, Upper respiratory tract infection, Urinary retention, Vital capacity decreased

Symptom Text: Pt admitted to hospital on 12/1/06 with chief complaint of ascending weakness bilaterally, upper and lower extremities. Neuro consult diagnosed Guillain-Barre syndrome. Pt received the Gardasil vaccine on 11/22/06. Resident MD asked pharmacist to write up possible ADR of Guillain-Barre from this vaccine. 02/21/2007 records received and reviewed for DOS:12/1/06-02/06/2007 DC DX:Severe form of Guillain-Barre syndrome after HPV vaccine and possible URI. Respiratory failure with prolonged mechanical ventilation and tracheostomy tube placement. Haemophilus influenzae, left lower lobe pneumonia, coag negative staph UTI. Hypertension. Tachycardia associated with dysautonomia now resolved. Presented to PCP with URI around Thanksgiving with associated sinus infection. Began having numbness and tingling in hands days of admission as well as back pain, headache and greater problems walking and began falling over. Able to wiggle her toes but with great difficulty. Pneumococcal vaccine in September/October. HPV vaccine on 11/22/06. Mother has possible MS and possible lupus. Neuro exam:Weakness of deltoid bilaterally, weakness of lower extremities with grade 4/5 weakness at hip flexor, 4/5 hip extension, 4/5 knee flexion, 4+/5 knee extension and 3+/5 plantar flexion. Deep tendon reflexes absent in all extremities even with augmentation. Plantar responses downgoing. Gait abnormal some degree of pelvic girdle weakness and foot drop bilaterally.Began IVIG. On day 2 began developing post void residuals. Vital capacity deteriorated on day 3 to 2.2 increasing difficulties with secretions as her gag and cough diminished. Able to move only jaw and eyes. Intubated and placed on fentanyl and versed. Developed HTN. Developed neuropathic pain. At discharge able to stand with assistance. Off vent on 1/26/07. Tachycardia and hypertension associated with autonomic dysfunction now resolved at discharge.

Other Meds: Zyrtec prn, guaifenesin prn, tylenol prn

Lab Data: Elevated protein in CSF; clinical symptoms suggestive of Guillain-Barre syndrome (primarily motor weakness, some altered sensation) Head CT normal except for sinusitis. Coag negative staph UTI. CSF: protein 64, glucose 57 and 7WBC. EMG on

History: None that I'm aware of

Prex Illness: I don't have this info

Prex Vax Illns:

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 305606-1 (D)

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
17.0	F	20-Feb-2008	22-Feb-2008	2	25-Feb-2008	26-Feb-2008	NY		26-Feb-2008

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	1968U	2	Left arm	Intramuscular	

Seriousness: DIED, SERIOUS

MedDRA PT Sudden death

Symptom Text: Sudden unattended death. Autopsy results pending (inconclusive 2/25/08).

Other Meds: Yasmin daily birth control

Lab Data:

History: No known drug allergies

Prex Illness:

Prex Vax Illns:

VAERS Line List Report

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 287888-1 (D)

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
22.0	F	21-May-2007	23-May-2007	2	13-Aug-2007	14-Aug-2007	--	WAES0708USA00407	14-Aug-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	0389U		Unknown	Intramuscular	

Seriousness: DIED, ER VISIT, SERIOUS

MedDRA PT Death

Symptom Text: Information has been received from a nurse practitioner concerning a 22 year old female patient with no pertinent medical history or drug allergies who on 21-MAY-2007, was vaccinated IM with a 0.5ml dose of Gardasil (Lot# 657736/0389U). Concomitant therapy included hormonal contraceptives (unspecified) ("MERCET"). On 23-MAY-2007, the patient died suddenly. The cause of death was unknown. Unspecified medical attention was sought. Laboratory diagnostic studies included an autopsy which showed no findings. No product quality complaint was involved. The reporter stated that Gardasil did not cause the patient's death. Additional information is not expected.

Other Meds: hormonal contraceptives

Lab Data: autopsy - no findings

History: None

Prex Illness:

Prex Vax Illns:

Vaers Id: 275990-1 (D)

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
Unknown	F	Unknown	Unknown		11-Apr-2007	12-Apr-2007	--	WAES0704USA00721	13-Apr-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL		Unknown	Unknown	

Seriousness: DIED, ER VISIT, SERIOUS

MedDRA PT Death, Thrombosis

Symptom Text: Information has been received from a physician's assistant (PA), via a company representative, concerning a female patient who was vaccinated (date unspecified) with a dose of Gardasil the PA reported that "the patient died of a blood clot 3 hours after getting the Gardasil vaccine." The PA clarified that the patient was not vaccinated at her office. Additional information has been requested.

Other Meds: Unknown

Lab Data: Unknown

History: Unknown

Prex Illness:

Prex Vax Illns:

Vaers Id: 275438-1 (D) **Related reports:** 275438-2

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
19.0	F	12-Mar-2007	26-Mar-2007	14	02-Apr-2007	03-Apr-2007	CA		07-Feb-2008

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	0263U	0	Left arm	Intramuscular	

Seriousness: DIED, SERIOUS

MedDRA PT Cor pulmonale, Coronary artery thrombosis, Echocardiogram abnormal, Pulmonary congestion, Pulmonary embolism, Pulmonary oedema, Sudden cardiac death, Thrombosis

Symptom Text: Given Gardasil vaccine dose #1 3/12/07. No adverse reaction reported. Collapsed and died on 3/26/07 secondary emboli (records unavailable). 4/3/07 Spoke w/investigating deputy who stated autopsy done at Medical Center. T/C to physician at Medical Center who is actually a cardiologist, not pathologist, who had responded to the code & pronounced. Spoke w/secretary who states from Death Certificate COD is sudden cardiac death and pulmonary embolism. Echocardiogram revealed very enlarged right ventricle & small left ventricle as well as large blood clots within both the right atrium & right ventricle. 6/25/07 Received Autopsy Report which reveals following anatomic diagnosis: 1. Pulmonary embolism, occlusive a. pulmonary trunk, left hilar & peripheral vessels b. acute cor pulmonale (by echocardiogram) 2. Pulmonary congestion & edema, bilatera a. no evidence of anomalous coronary artery distribution b. no evidence of ventricular dysplasia

Other Meds:

Lab Data:

History: None

Prex Illness: None

Prex Vax Illns:

Vaers Id: 280163-1 (D)

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
11.0	F	01-May-2007	04-May-2007	3	01-Jun-2007	04-Jun-2007	--	WAES0705USA04839	04-Jun-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL	0	Unknown	Unknown	

Seriousness: DIED, ER VISIT, LIFE THREATENING, SERIOUS

MedDRA PT Anaphylactic reaction, Cardiac arrest, Death

Symptom Text: Information has been received from a nurse practitioner who heard from an emergency room (ER) nurse that an 11 year old female was vaccinated "within in the past month" in approximately May 2007 with a first dose of Gardasil. Subsequently, 3 days after vaccination the patient presented to an ER. She experienced cardiac arrest, required lung bypass (ECMO) and "may not have expired." It was also reported by the same nurse that the physician from the hospital said that "the death was due to an anaphylactic reaction to Gardasil." The anaphylactic reaction and cardiac arrest were considered to be life threatening by the reporter. Additional information has been requested.

Other Meds: Unknown

Lab Data:

History: Unknown

Prex Illness:

Prex Vax Illns:

VAERS Line List Report

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 300741-1 (D) **Related reports:** 300741-2

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
18.0	F	22-May-2007	23-May-2007	1	21-Dec-2007	26-Dec-2007	FR	DEPEIPEI2007006990	26-Dec-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL	1	Unknown	Unknown	

Seriousness: DIED, SERIOUS

MedDRA PT Brain oedema, Death, Hypoxia, Intracranial pressure increased, Loss of consciousness, Pulmonary haemorrhage, Pulmonary oedema, Resuscitation

Symptom Text: Case narrative including clinical course, therapeutic measures, outcome and additional relevant information: Case initially received on 12-Jun-07. It was reported by a sales representative who was informed by a gynaecologist (who himself had heard of the case from another gynaecologist) that a 18-year-old female patient was vaccinated with the first dose of Gardasil (lot # and injection route and site not reported) on an unspecified date beginning June 2007 (week 23). In the evening of the same day she was found unconscious (or liveless) by the mother. Resuscitation was performed by the emergency doctor but was unsuccessful, i.e. the patient finally died. To be noted is an anamnesis of dental surgery. Follow-up 10.10.2007: results of autopsy. History: this female patient collapsed from total health status at home. After 3 hours of reaminmation the patient was declared dead. To be noted is an anamnesis of dental surgery. Follow-up 10.10.2007: results of Autopsy history: This female patient collapsed from total health status at home. After 3 hours of reaminmation the patient was declared dead. In the recent history the patient had dental surgery about two to three weeks ago. First vaccination with Gardasil 27.03.2007, second vaccination 1 day before the exitus (22.05.2007). Both times the patient had not felt bad and had not reported of any side-effects. Cause of Death: not definitely clear, results of makroskopic examination of the heart could be a hint for a myocarditis (flaccid muscle with different couloured spots - fleckig-scheckige Zelchnung). For clarification whether the patient died of myocarditis a histological examination was done. Results of histological examination: Suspected diagnose of myocarditis could not be supported. This patient did not have a myocarditis. Concluding results of the autopsy: the cause of death of this patient remain totally unclear. The following reasons for death of this patient can be excluded sepsis or any inflammatory reason e.g. due to the dental surgery, or anaphylactic rea

Other Meds:

Lab Data:

History: Dental surgery NOS

Prex Illness:

Prex Vax Illns:

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 299377-1 (D)

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
19.0	F	19-Sep-2007	05-Oct-2007	16	12-Dec-2007	13-Dec-2007	FR	WAES0712USA01347	13-Dec-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	1475F	0	Unknown	Unknown	

Seriousness: DIED, SERIOUS

MedDRA PT Bronchitis, Death, Diarrhoea, Photophobia

Symptom Text: Information has been received from a gynecologist concerning a 19 year old female with no previous medical history reported, who on 19-SEP-2007 was vaccinated (route and site not reported) with the 1st dose of Gardasil (Batch# NF37120, lot#1475F). On the morning of 12-OCT-2007, the patient was found dead in her bed. One week prior to death the female suffered from diarrhea, treatment without antibiotics. The patient also developed light sensitivity. The evening before the patient died she was out with a girlfriend until 3:00 am in the morning. The reporting physician excluded any drug misuse, as she knew the female as a sportive young woman. Contraception was stopped 3 months before vaccination. No reason for the death was detected in autopsy. The only finding in the autopsy was mild bronchitis and mucus. The reporting physician excluded any connection between vaccination and death. Other business partners numbers include E2007-08849(0). Additional information is not expected.

Other Meds: Unknown

Lab Data: Unknown

History: None

Prex Illness:

Prex Vax Illns:

Vax Type: HPV , HPV4 (Comb. w/OR) Reported Date: 07-JUL-07 - 27-MAR-08 All comb. w/AND

Vaers Id: 297528-1 (D)

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
12.0	F	15-Sep-2007	06-Oct-2007	21	23-Nov-2007	26-Nov-2007	--	WAES0711USA02619	26-Nov-2007

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	NULL		Unknown	Unknown	

Seriousness: DIED, LIFE THREATENING, SERIOUS

MedDRA PT Death

Symptom Text: Information has been received from a physician's assistant concerning a 12 year old female with no reported medical history who on approximately 15-SEP-2007 was vaccinated with Gardasil. It was noted that this was not where the vaccine was administered, rather they were the patient's family physician. On 06-OCT-2007 the patient died in her sleep. No further information was provided. No lot number was given. Additional information has been requested.

Other Meds: Unknown

Lab Data: Unknown

History: Unknown

Prex Illness:

Prex Vax Illns:

Vaers Id: **305606-1 (D)** **Related reports:** 305606-2; 305606-3

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
17.0	F	20-Feb-2008	22-Feb-2008	2	25-Feb-2008	26-Feb-2008	NY		06-May-2008

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	1968U	2	Left arm	Intramuscular	

Seriousness: DIED, SERIOUS

MedDRA PT Arrhythmia, Electrocardiogram QT prolonged, Fall, Laceration, Sudden death

Symptom Text: Sudden unattended death. Autopsy results pending (inconclusive 2/25/08). 2/26/08 Reviewed pcp medical records & vax records which reveal patient received HPV#1 0469U 7/16/07 & HPV#2 09300 9/17/07. In 11/20/07, noted to have left sided head pain intermittently along with lightheadedness; dx w/tension HA. HPV#3 was scheduled for 1/16/2008 but postponed due to no parental signature. Returned to office 1/24/08 for left wrist pain from cheerleading injury s/p ER vs for same on 1/19/08. Patient last seen in office by nurse only on 2/20 for HPV #3, no notes for visit. PMH: kicked in face by horse in past (undated) & had contusion on cheek; acne vulgaris, started Yasmin & topicals 4/07 w/improvement after multiple other drug failures; 1/19/08 wrist contusion from cheerleading. 5/2/08 Autopsy report states COD as undetermined. Autopsy states patient had intermittent HAs x 2 mo & had been on BCP x 1 year for acne. Found w/small facial laceration from striking flower pot when fell. The autopsy was neg for all findings. Scene indicated sudden death from collapse & fall. Suspected long QT interval syndrome w/fatal arrhythmia rather than new onset seizure in patient w/no history of either. Suggested testing family members.

Other Meds: Yasmin daily birth control

Lab Data:

History: No known drug allergies

Prex Illness:

Prex Vax Illns:

Vaers Id: 310262-1 (D)

Age	Gender	Vaccine Date	Onset Date	Days	Received Date	Status Date	State	Mfr Report Id	Last Edit Date
20.0	F	01-Apr-2008	05-Apr-2008	4	21-Apr-2008	22-Apr-2008	NC	WAES0804USA02336	25-Apr-2008

VAX Detail:	Type	Manufacturer	Lot	Prev Doses	Site	Route	Other Vaccine
	HPV4	MERCK & CO. INC.	1978U		Unknown	Unknown	

Seriousness: DIED, ER VISIT, LIFE THREATENING, PERMANENT DISABILITY, SERIOUS

MedDRA PT Death

Symptom Text: Information has been received from a physician concerning a 20 year old female with no medical history reported, who on 01-APR-2008 was vaccinated with a dose of Gardasil. On 05-APR-2008, the patient died four days after receiving Gardasil. The patient sought unspecified medical attention. An autopsy was performed which ruled out suicide and anything suspicious. The cause of death is currently unknown and they are performing toxicology tests to try to determine the cause. No product quality complaint was involved. The reportable physician considered death to be immediately life-threatening and disabling. Additional information has been requested.

Other Meds: Unknown

Lab Data: autopsy, 04/??/08, ruled out suicide or anything suspicious; diagnostic laboratory, 04/??/08, toxicology results unknown

History: None

Prex Illness:

Prex Vax Illns:

Tab C

Relevant Excerpt, Pages 11 – 32 of original transcript

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

+ + + + +

VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

+ + + + +

MEETING

+ + + + +

THURSDAY,
MAY 18, 2006

+ + + + +

The meeting convened at 9:00 a.m. in Salons A, B, and C of the Hilton Washington D.C. North/Gainthersbury, 620 Perry Parkway, Gaithersburg, Maryland, Monica M. Farley M.D., Acting Chair, presiding.

ADVISORY COMMITTEE MEMBERS PRESENT:

MONICA M. FARLEY, M.D.	Acting Chair
SCOTT EMERSON, M.D., Ph.D.	Temporary Voting Member
BRUCE GELLIN, M.D., M.P.H.	Temporary Voting Member
MICHAEL GREENE, M.D.	Temporary Voting Member
SUSAN KRIVACIC	Temporary Voting Member
PHILIP S. LaRUSSA M.D.	Member
SAMUEL MALDONADO, M.D.M.P.H.	Acting Industry Rep
LAURI MARKOWITZ, M.D.	Non-Voting Member
PAMELA McINNES, D.D.S.	Temporary Voting Member
KENNETH NOLLER, M.D.	Temporary Voting Member
CINDY PROVINCE, R.N. M.S.N.	Consumer Representative
WALTER ROYAL, III, M.D.	Member
ELIZABETH UNGER, M.D.,Ph.D.	Temporary Voting Member
MELINDA WHARTON, M.D., MPH	Temporary Voting Member
BONNIE WORD, M.D.	Member

FDA STAFF PRESENT:

CHRISTINE WALSH, R.N.	Executive Secretary
NANCY MILLER, M.D.	Medical Officer, Office of Vaccine Research and Review, Division of Vaccines and Related Products Applications
KAREN GOLDENTHAL, M.D.	
HENRY HSU, Ph.D. M.P.H.	
HECTOR IZURIETA, M.D.	
JOSEPH TOERNER, M.D. M.P.H.	

SPONSOR PRESENTERS:

ELIAV BARR, M.D.	Senior Director, Vaccines/Biologics Clinical Research, Merck & Co., Inc.
PATRICK BRILL-EDWARDS, M.D.	Director, Worldwide Vaccines Regulatory Affairs, Merck & Co.
JANINE BRYAN	
ADRIAN DANA	
LAURA KOUTSKY, Ph.D.	University Washington
MYRON LEVIN, M.D.	University of Colorado
LISA LUPINACCI	

PUBLIC HEARING SPEAKERS:

AMY ALLINA	National Women's Health Network
DEBORAH ARRINDELL	American Society Health Association
BOBBIE S. GOSTOUT, M.D.	Society of Gynecologic Oncologists
KATHRYN GUCCIONE	Women in Government
SUSAN E. HOLLERAN	Coalition of Labor Union Women
BETH JORDAN, M.D.	Medical Director, Association of Reproductive Health Professionals
KRISTEN MOORE	Reproductive Health Technologies Project
MARTHA NOLAN	Society for Women's Health Research
ELLEN STOVALL	National Coalition for Cancer Survivorship
SEAN TIPTON	American Society for Reproductive Medicine

DR. BRILL-EDWARDS: Good morning and thanks for attending. We're here today to share results of clinical trials using Gardasil, which is Merck's quadrivalent human papillomavirus vaccine. This vaccine is currently receiving a priority review because of its potential to meet an un-met medical need.

Now, in the health sciences, there is nothing more rewarding than being able to contribute to meeting an un-met medical need. I'd like to draw your attention to a comment Sir Isaac Newton made to a colleague who was complimenting him on his contributions to science, and that's that, if I have seen further, it's by standing on the shoulders of giants.

Now, in our case, we are standing on the shoulders of the basic scientists whose observations about this virus led to the concept to the vaccine and to the many clinicians and scientists who developed and implemented the successful cervical cancer screening programs that we have today.

We're excited about these results because Gardasil has the potential to build on the success of cervical cancer screening programs and provide clinicians with the first vaccine to prevent cervical cancer. After this brief overview, Dr. Eliav Barr will present a detailed discussion of our results

In general, Gardasil is a vaccine indicated for the prevention of cancer, pre-cancerous or dysplastic lesions, genital warts and infection caused by the HPV types targeted by the vaccine.

Cervical cancer is caused by HPV. HPV infection is common. Life-time risk for infection is 50 percent. In the U.S. the life-time risk for developing Cervical Intraepithelial Neoplasia or CIN, is 25 percent and over 10 percent of adults will develop genital warts due to HPV.

Cervical cancer is the second most common cancer in women worldwide. There will be approximately a half a million new cases and 290,000 deaths each year. Despite Pap screening, American women remain at risk. There will be approximately 10,000 new cases each year, 3,700 deaths, or put another way, 10 American women will die each day from cervical cancer.

There is currently no approved vaccine for the prevention of cervical cancer. Therefore, an Advisory Committee, very similar to today's procedure, was convened in 2001 to consider the clinical endpoints that would serve as

the basis for licensure.

At that time, Merck proposed that studying cancer itself isn't feasible, because it takes too long and it disadvantages too many women. We also had to consider that most HPV infections in pre-cancers regress. So, there was the need to consider an endpoint that had a direct link to cancer. And pointing to the success of cervical cancer screening programs, their success is due to the detection and definitive therapy for CIN 2/3, and that's what we recommended as the basis of licensure and ultimately, that's what the Advisory Committee recommended.

To profile the vaccine, as I mentioned, it's a quadrivalent. It contains four HPV types. Two types, 16 and 18, are so-called high-risk because they're responsible for 70 percent of cervical cancers. The other two types, six and 11, though not commonly associated with cancer, are responsible for 90 percent of genital warts.

The virus-like particles that we use are manufactured in yeast, which is a well-established vaccine manufacturing method and it's absorbed to Merck's aluminum-hydroxy-phosphate-sulfate, which has a well-established safety record. The vaccine is intended to be used in a three dose regimen at zero, two and six months. It's not a live-virus vaccine and therefore, the VLP's cannot cause infection or disease.

To review a brief overview of what a VLP looks like, on the left side of the slide, you'll see the L1 proteins that are produced and then they self-assemble into pentamers, also known as capsomeres, and a typical VLP represents 72 to of these capsomeres in a hollow sphere. It's this hollow sphere that the immune system sees.

To preview Dr. Barr's presentation, we've studied Gardasil in over 27,000 subjects in 33 countries. Gardasil, like all vaccines, is most effective when given before exposure to infection. In that prophylactic setting, Gardasil is efficacious and it's this high efficacy that forms the basis of the priority review. The vaccine is immunogenic, it induces an immune response that's many-fold higher than natural infection and it has an excellent safety profile.

Specifically, Gardasil is indicated for the prevention of the following, due to types 16 and 18, cervical cancer, cervical adenocarcinoma in situ, CIN 2/3, vulvar and vaginal cancer, VIN grades 2 and 3, VaIN grades 2 and 3, but also, it's indicated for the following, due to all vaccine types, CIN 1, genital warts, VIN 1, VaIN 1 and HPV infection.

To remind you, cervical cancer is caused by the

human papillomavirus. Gardasil prevents disease caused by the most common HPV types and Gardasil has the potential to meet an un-met medical need as the first vaccine to prevent cervical cancer.

Merck has several consultants in attendance today and I'd just like to acknowledge them. We have Dr. Laura Koutsky, Professor of Epidemiology from the University of Washington. We have Dr. Michael Cunningham who is the head of the Cranial Facial Medicine Program, also at the University of Washington. We have Dr. Mark Stoler, a Professor of Pathology from the University of Virginia. Dr. Myron Levin, Professor of Pediatrics from the University of Colorado and Dr. Janet Wittes, who is the President of Statistics Collaborative.

And now, I'd like to ask my friend and colleague, Dr. Eliav Barr to give you a detailed discussion of our results.

DR. BARR: Good morning. My name is Eliav Barr. I'm head of the clinical program for Gardasil, Merck's quadrivalent HPV vaccine. I really wanted to thank the Committee for the opportunity to present the results of our clinical program.

Merck's HPV vaccines have been in clinical trials for over nine years. The program has enrolled over 27,000 women and children in 12 separate clinical studies. To summarize this comprehensive clinical program, I'd like to spend a few minutes reviewing the clinical significance of the disease, talk a little about how we designed the clinical program to address efficacy, immunogenicity and safety, provide an overview of the keys findings with regards to efficacy, immunogenicity and safety, and then describe all of this data into the overall very favorable benefit risk profile for Gardasil.

Now, HPV is a potent carcinogen. It tends to infect the squamocolumnar junctions of the genital tract, the anal mucosa and the aero-digestive track. On infection, the virus causes disordered cellular proliferation, which can result in malignant degeneration.

HPV infection is necessary for the development of cervical cancer. All cervical cancers arise from HPV infected tissue. HPV is also an important contributor to cancers of the genital tract in both women and men and is an important contributor to certain head and neck cancers.

Now, HPV also causes benign tumors, including low-grade cervical vulvar and vaginal dysplasia that are the most common reasons why women have Pap test abnormalities, genital warts and recurrent respiratory papillomatosis, which

are rare diseases, but very devastating, warty tumors of the larynx.

Now, these lesions are not malignant, but they cause enormous amounts of morbidity and a lot of health care costs.

HPV is the most common sexually transmitted infection world wide. Over 50 percent of Americans will become infected with HPV at some point in their life times. In women, this infection is manifested by the third of cases in CIN, grade 1, cervical intraepithelial neoplasia, grade 1 or low-grade dysplasia. So, the life time risk of this lesion in American women is one in six.

A smaller proportion of women will develop CIN 2/3 or AIS, that's cervical intraepithelial neoplasia, grade 2/3, moderate to high-grade, cervical pre-cancer or adenocarcinoma in situ.

In the absence of cervical cancer screening, the life time risk of cervical cancer is about one in 30. Pap testing and other means of screening have reduced the risk of cervical cancer in countries where screening is available from -- by about 75 percent, so that's decreased the risk from about one in 30, to about one in 120.

As I mentioned, HPV also causes genital warts and about one in eight, men and women, in the U.S. will develop a case of genital warts at some point in their lives.

Cervical cancer is the most important disease caused by HPV infection. Around the world it's the second most common cause of cancer in women. Eight-hundred women will die every day from cervical cancer world wide. Cervical cancer mortality and morbidity. The impact on society is accentuated by young age of its victims.

There are two kinds of cervical cancer, both of which are completely HPV related. Eighty percent is squamous cell variant, and that's proceeded by CIN lesions, and about 20 percent are adenocarcinomas and those are proceeded by adenocarcinoma in situ. It's worth noting that adenocarcinoma rates have been increasing in the United States over the past years because Pap testing doesn't detect this kind of cancer very well and HPV infection rates have been increasing in the population.

Now, Pap testing and HPV testing, more recently, has been in a very important public health program and has reduced the rate of cervical cancers by 75 percent in the U.S. But there is significant costs associated with this approach. HPV infection is very frequent, so women have to be screened frequently, and that translates to approximately 50 million Pap tests every year that yield about three and a

half million Pap test abnormalities every year in the U.S., which require some form of follow-up and that leads to the diagnosis of 1.4 million cases of CIN 1 or low-grade dysplasia and 330,000 cases of CIN 2/3, all of which require substantial amount of follow-up and treatment.

In addition to the morbidity that it causes to women, these lesions -- and screening programs are very expensive. They cost over four billion dollars a year in the U.S. every year.

Now, despite the availability of screening, around 10,000 American women will develop cervical cancer. The reasons for this is either non-compliance with screening, lack of regular availability for health care, or the inherent limitations of the sensitivity of the Pap test. And this 10,000 rate means about 10 American women will die of cervical cancer every day.

HPV also causes vulvar and vaginal cancer at around 40 or 50 percent. That translates to around 3,500 cases a year. These lesions are very similar in natural history to cervical cancer and it's also worth noting that the instance of vulvar cancer in the U.S. has increased in women less than 50, again, due to the increased incidents of HPV infection that then results in vulvar dysplasia and cancer.

Now, HPV infection also causes cancer in men and the sources of those cancers are shown here. About 10,000 American men will develop an HPV related cancer every year in the U.S., mostly in the head and neck, anal canal and the penis.

As I mentioned, HPV causes genital warts. The life time risk exceeds 10 percent in both men and women. That means in the U.S., about a million new cases a year in American men and women.

Now, these lesions are not malignant, but they are very painful and they are very psychologically damaging, particularly to young people who tend to get them.

Treatment is also unsatisfactory. The visible genital warts is really the tip of the iceberg of a much broader field infection that therefore, requires significant rounds of therapy with ablation. It's very difficult to get rid of them. Typically you need three rounds of therapy and even then, 30 percent of these lesions recur. So, this is pretty substantial public health problem.

And finally, HPV also causes recurrent respiratory papillomatosis. This is a really devastating disease, due to infection of the vocal folds in the larynx with HPV types. It causes hoarseness and airway obstruction

and that airway obstruction requires quite a bit of surgery.

There are two types of binormal-distribution of RRP, a juvenile variant and an adult variant. The juvenile variant occurs in boys and girls age three to four, roughly. It's a very, very aggressive disease that requires on average, four separate surgeries every year to clear the airway obstruction and make sure that the person can breathe, and malignant transformation can spread to the lung and other organs in the airway and is not uncommon. Adult RRP is also quite a significant public health problem. Typically, it occurs in people in their 20's and 30's.

So, I think I've shown you that HPV infection causes significant amount of morbidity and mortality in the U.S. Every year over four million Americans are impacted by a new diagnosis of an HPV related disease.

HPV is a highly endemic infection and prophylactic vaccination is an excellent way to prevent highly endemic infectious diseases and on the basis of that, Merck decided to develop a prophylactic HPV vaccine.

And the technology that we decided to use was based on the observation that when the L1 capsa protein, the outer coat protein of the virus, is expressed in recombinant systems, it self-assembles into a virus-like particle that looks just -- very similar to the wild-type virus, without of course, the infectious properties. And in animal models of papillomavirus infections using these L1 VLP's, we were able to show that vaccination resulted in protection from infection disease, but neutralizing antibodies were induced, and most importantly that when you transfer serum from vaccinated animals to unvaccinated animals, you also transfer protection. And that just demonstrated the critical importance of humeral immunity and circulating antibodies in the way in which this vaccine mediates its efficacy.

So, on the basis of these promising preliminary observations, we developed a very stable technique to manufacture highly purified L1 VLP's using recombinant yeast technology. This technology has been used in a variety of vaccines that have been given in hundreds of millions of doses to infants, children, adults around the world over the past 20 years.

So, the vaccine that we chose to develop is Gardasil. Gardasil covers the HPV types that are responsible for the majority of clinical HPV disease in the U.S. The four type are HPV 16 and 18, and six and 11. These two are the cancer causing HPV types, that are responsible for 70 percent of the all of the HPV related cancers in both men and women and they're also responsible for the majority of the

high-grade pre-cancerous lesions. Also, they are responsible for 25 percent of low-grade dysplastic lesions. These are the very common lesions that are the major finding when women have a Pap test abnormality.

Now, HPV 16 and 18 infection in men, not only causes cancer in men, but it also the primary means of transmission of this malignant HPV type to women.

HPV six and 11 together cause about 90 percent of genital warts in women and men, as well as 90 percent of RRP lesions. Of note, they also cause 10 percent of the CIN 1 lesions and these are clinically indistinguishable from the CIN 1 lesions that are caused by the high-risk types. So, here women are told that they have a pre-cancerous lesion, when in fact, no such risk exists.

And then again, HPV six and 11 infection in men, not only impacts men, but it's, men are the primary vector for transmission of HPV to women and again, infection in men is the cause of the acquisition of disease in women.

So, a vaccine that targets these four HPV types would target a large burden of HPV infection and a successful vaccine would really reduce the burden of HPV disease in the U.S.

And so, once we chose to evaluate this particular vaccine, we set about to design a clinical program that would address the key issues in terms of the prophylactic efficacy of this product. And I wanted to share a little bit about that with you on the rational of the clinical program and why we chose the particular studies that we did.

Now, at the inception of the phase three program, Merck and FDA met and agreed that the primary basis for licensure was to -- was based on the demonstration of the prophylactic efficacy of Gardasil, to show that Gardasil is efficacious in preventing HPV 16 and 18 and related cervical cancer. That would be the primary basis for licensure. We also discussed a variety of different end points.

We also understood that the studies would continue and that separate from licensure, we would do supplemental analysis at the end of the phase three program, not only to look at the impact of the vaccine on type-specific disease, but also to get a clearer picture of the impact of Gardasil on the overall burden of clinical HPV disease, regardless of the causal HPV type. And those analysis will be available next year.

In 2001, the VRBPAC Committee of -- at the time, met to discuss the basis for licensure of prophylactic HPV vaccines. And it was obvious to everybody that the key benefit that such vaccines might provide is prevention of

cervical cancer. But it was also obvious to the Committee that that end point wouldn't work in a clinical trial setting. First of all, although HPV infection is necessary for the development of cervical cancer, there is a long time delay between infection and the development of cancer.

But more importantly, it was clear that those studies -- that any studies that would be done would require very intensive Pap testing and the best possible screening opportunities for women who participate in this study. And so, most of the cervical cancers would then be detected at the CIN 2/3 or AIS stage and would be excised as per standard practice, and so, we would never be able to reach the cervical cancer end point.

So, the Committee looked at earlier end points and the first one that they considered was HPV infection. After all, it's a necessary pre-requisite to cervical cancer. But most HPV infections clear and so, it wasn't clear whether or not we would prevent the types of infection that would lead to cancer.

They looked at CIN 1 and in deed, these lesions also tend to clear. They are also not on the critical path to cervical cancer.

So, attention focused on CIN 2/3 or AIS. These are the targets of cervical cancer screening, and we know that the way in which Pap testing works in HPV testing, is that it allows physicians to detect CIN 2/3 or AIS and to excise those lesions before they progress to cervical cancer. And in countries where this is the only lesion that's treated, the rates of reduction in cervical cancer, mediated by cervical cancer screening, is the same as in countries where more aggressive approaches are used.

So, it was clear that this is the way in which Pap testing works. And so, if a vaccine could prevent these lesions from occurring from the outset, we would be able to demonstrate the efficacy of the vaccine with respect to cervical cancer, and that's what is the primary objective of the program, to demonstrate that the vaccine prevents the development of HPV 16 and 18 related CIN 2/3 and AIS caused by new infections.

The rational for the vulvar and vaginal cancer end point really followed the same approach that we used for the cervical cancer end points, and this is because HPV related vulvar and vaginal cancer have a very similar natural history studies. They all arise from HPV infected highly dysplastic tissue. And in case series of un-treated VIN or treated VaIN 2/3, the rates of progression to cancer were actually quite substantial, 16 percent of every interval of

3.9 years and two percent over two years. So, these are excellent surrogate markers for vulvar and vaginal cancers related to HPV.

We had also key immunogenicity and safety objectives. The most important one was to bridge the efficacy findings in 16 to 26 years olds, to nine to 15 year old pre-adolescents.

Now, Gardasil is a prophylactic vaccine. It will be most effective when it's administered to populations prior to entry into the risk period, and that's the age group 15 and below.

Now, we also knew that it was not feasible to do efficacy studies in this population because of limitations on discussions of sexuality and of HPV sampling in very young pre-adolescents. So, FDA and Merck agreed that we could bridge the efficacy findings in 16 to 26 year old to the younger age range using immuno-bridging approaches.

Immunogencity was also used for -- to evaluate the duration of efficacy and immune response to Gardasil, as well as to examine how the vaccine interacts with other common adolescent vaccines.

A critical parameter of our clinical program was safety and we sought to comprehensively define the safety program of Gardasil and all of the populations for which the vaccine would be indicated.

We also knew that this vaccine would be given to women of child-bearing potential, so right from the beginning, we set up a program that would really evaluate in great detail, all the pregnancy outcomes that would occur and subject to receive Gardasil, regardless of the temporal association between the time that they received the vaccine and the time that they became pregnant. So, throughout the course of the clinical trials.

Now, I have alluded to the various age ranges of the clinical program, and I wanted to explain why we chose this particular age range, and the way that I wanted to explain it is by showing you when HPV infection hits the population. And the way that I'm showing you this is by the incidents of new genital warts in the large private insurer data base in the U.S. And I choose genital warts as a marker for HPV infection because they happen very quickly after infection starts and also, it's very detectable. People know when they have genital warts and they can immediately report it. So, it's a really good marker of the temporality of the infection relative to age.

And what you can see is, you can see the age by different buckets here and the new case rates, males and

females, and in the early teens, there's very little genital warts, very little HPV infection. But starting with the time of sexual debut, there's just an enormous increase in the risk of these diseases and the peek age is in 16 to 26 year olds, and that's where we chose to do our main efficacy studies, 16 to 26 year old women.

And for the immuno-bridging analysis we evaluated nine to 15 years old, the period just prior to entry into the period of acquisition of HPV infection. And so, what we were looking for is an indication for the vaccine to be used in nine to 26 year old age range.

We also knew that this program would last for several years. We wanted to look at long term duration of efficacy. We also wanted to evaluate the vaccine in a large population of subjects. And so, we decided to develop a clinical info-structure that would really allow us to combine all studies together and to have consistent ascertainment of safety and efficacy over a long period of time.

So, we trained the investigators to use a standardized approach to collection of specimens. The same approach was used in all clinical trials. Central pathology laboratory was used for all cytology and pathology work. Everything was processed through our central lab. HPV detection was done in one location in one laboratory. We had a validated pathology panel whose sole responsibility was to read slides for the purpose of end point evaluation. And then a large data -- the data sifting monitoring board was used in all the large clinical trials. And so, together we were able to ensure that we had accurate and complete representation of the efficacy end points, as well as safety.

Tab D

Relevant Excerpt, Pages 9 – 12 of original document

Patrick Brill-Edwards, M.D., F.A.C.P.
Director
Worldwide Regulatory Liaison
Vaccines/Biologics

Merck & Co., Inc.
P.O. Box 4, BLB-22
West Point PA 19486
Tel 484 344 7883
Fax 484 344 2962
patrick_brilledwards@merck.com

April 19, 2006

MERCK
Research Laboratories

Christine Walsh, R.N.
FDA/CBER/DSAC/HFM-71
5515 Security Lane
Rockwall II Building, Room 1113
Rockville, MD 20852

Dear Ms.Walsh:

GARDASIL™
Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine
STN 125126

Find enclosed 35 copies of the final briefing document for the upcoming GARDASIL™ Vaccines and Related Biological Products Advisory Committee meeting to be held on May 18, 2006. By receipt of this letter Merck & Co., Inc. hereby grants permission to allow the Food and Drug Aministration (FDA) to make this document public and to allow the FDA to post is on the FDA website without redaction. A Compact Disc is also being provided for the sole purpose of posting on the aforementioned website.

Merck has taken precautions to ensure that the contents of the media are free of computer viruses (Symantec AntiVirus Corporate Edition, Symantec Corporation), and we authorize the use of anti-virus software, as appropriate.

Questions concerning this application should be directed to me at (484-344-7883) or, in my absence, to Ercem Atillasoy at (484-344-7811).

Sincerely,

Patrick Brill-Edwards, M.D.
Director
Worldwide Regulatory Affairs
Vaccines/Biologics

Attachments

DHL

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse experience
AIN	Anal intraepithelial neoplasia
AIS	Adenocarcinoma in situ
ASC-H	Atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of unknown significance
BLA	Biologics Licensing Application
BMI	Body mass index
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
cLIA	Competitive Luminex immunoassay
cRIA	Competitive radioimmunoassay
CSR	Clinical study report
DAP	Data analysis plan
DNA	Deoxyribonucleic acid
ECC	Endocervical curettage
EGL	External genital lesion
EOP	Estimated onset of pregnancy
GMT	Geometric mean titer
H&E	Hematoxylin and Eosin
hCG	Human chorionic gonadotropin
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
LEEP	Loop electroexcision procedure
LSIL	Low-grade squamous intraepithelial lesion
mAb	Monoclonal antibody
MITT	Modified intention-to-treat
mMU/mL	Milli Merck units per milliliter
MRL	Merck Research Laboratories
Pap	Papanicolaou's test
PCR	Polymerase chain reaction
PPE	Per-protocol efficacy
PPI	Per-protocol immunogenicity
PV	Papillomavirus
RRP	Recurrent respiratory papillomatosis
SIL	Squamous intraepithelial lesion
SUR	Safety update report
VaIN	Vaginal intraepithelial neoplasia
VIN	Vulvar intraepithelial neoplasia
VLP	Virus-like particles
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VRC	Vaccination report card

1. Introduction and Organization of the Document

An original Biologics Licensing Application (BLA) for the use of GARDASIL®[1] (human papillomavirus [Types 6, 11, 16, 18] recombinant vaccine) was filed by Merck & Co., Inc. in December 2005. The application has received priority review status. This document provides a summary of the safety, efficacy, and immunogenicity data to support licensure of this vaccine.

GARDASIL® is a vaccine intended to prevent anogenital cancers and their precursor lesions, genital warts, and infection caused by the human papillomavirus (HPV) types 6, 11, 16, and 18. These HPV types cause the majority of genital HPV disease in the United States.

The clinical development program for GARDASIL® included girls and women 9 to 26 years of age and boys 9 to 15 years of age at the start of vaccination. This range covers the period just prior to sexual debut through the period of peak risk for HPV infection. Subjects were enrolled regardless of baseline HPV status, as vaccination programs will be population-based (no HPV screening prior to vaccination). Inclusion of subjects with prior or ongoing HPV infection also allowed for an evaluation of the impact of such infection on the efficacy, immunogenicity, and safety of GARDASIL®. The clinical program was conducted in 5 continents and 33 countries, providing diversity that justifies the application of study findings to the general population of 9- to 26-year-old subjects worldwide.

Efficacy was assessed in 4 randomized, double-blind, placebo-controlled studies. Together, these trials randomized 20,887 16- to 26-year-old adolescent and young adult women, of whom 20,845 subjects received at least one dose of vaccine (GARDASIL®, HPV 16 L1 VLP vaccine component of GARDASIL®, or placebo). Overall, 19,321 subjects (92.7% of subjects who received at least one dose of vaccine) continued in the study from the time of enrollment through the date at which each study's database was closed.

The immunogenicity studies for GARDASIL® evaluated anti-HPV responses 1 month after the completion of the 3-dose vaccination regimen and for up to 3.5 years thereafter. In these trials, 12,344 subjects (9- to 26-year-old girls and women; 9- to 15-year-old boys) were randomized to receive GARDASIL® or placebo. Of these, 11,726 completed the vaccination phase of the studies. Trials that enrolled 9- to 15-year-old subjects served 2 purposes: (1) to bridge efficacy findings from mostly sexually active 16- to 26-year-old subjects in whom efficacy was evaluated to adolescents prior to sexual debut in whom efficacy trials are not feasible; and (2) to demonstrate that anti-HPV responses induced by GARDASIL® in boys are non-inferior to those generated in girls (gender-neutral vaccination programs will be needed to induce herd immunity). Other trials were

[1] GARDASIL is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

designed to: (1) show that GARDASIL® can be given concomitantly with hepatitis B vaccine (both vaccines are given to adolescents); (2) show the consistency of manufacture of GARDASIL®; and (3) provide data to support dose justification for manufactured lots of GARDASIL®.

The safety of GARDASIL® and its monovalent precursors was assessed in 12 studies in which 16,014 subjects received at least one dose of HPV L1 VLP vaccines (of these, 11,792 subjects receiving GARDASIL®). The safety of GARDASIL® was evaluated with regard to: (1) injection-site and systemic tolerability; (2) impact on long-term health status; and (3) interaction with pregnancy and lactation, events that are likely to occur in the population for which GARDASIL® will be indicated.

The clinical program for GARDASIL® has shown that the vaccine is highly efficacious in preventing the development of cervical cancer, vulvar cancer, vaginal cancer, the dysplastic lesions preceding these cancers, and genital warts caused by vaccine HPV types in a broad population of subjects who were representative of the population in which GARDASIL® is intended. Efficacy was durable through at least 2.5 years postvaccination with respect to infection and disease caused by HPV 6, HPV 11, and HPV 18, and at least 3.5 years postvaccination with respect to infection and disease caused by HPV 16. Phase III study subjects in the Nordic Region will be followed for up to 15 years to define the longer-term efficacy of GARDASIL®. Because these subjects completed their vaccinations in 2003, the longer-term duration of efficacy of the vaccine will be known well in advance of the time needed to implement booster vaccinations in the general population (if such boosters are required).

GARDASIL® was highly immunogenic in all populations tested, inducing robust anti-HPV responses regardless of gender, ethnicity, national origin, body mass index (BMI), smoking status, Day 1 Papanicolaou (Pap) test result, lifetime number of sexual partners at enrollment, and method of contraception used prior to vaccination. Based on the numerically superior and statistically non-inferior anti-HPV responses induced by GARDASIL® in 10- to 15-year-old boys and girls compared with 16- to 23-year-old adolescent and young adult women, the efficacy of GARDASIL® can be bridged from 16- to 23-year-old female subjects in whom efficacy was evaluated with virginal adolescents in whom an efficacy evaluation was not feasible. Concomitant administration of GARDASIL® with RECOMBIVAX HB®[2] (hepatitis B vaccine, recombinant) resulted in anti-HPV levels and anti-HBs levels that were comparable to those observed when these vaccines are administered nonconcomitantly.

The clinical program has shown that GARDASIL® has an excellent safety profile. GARDASIL® was generally well tolerated in all groups tested. Vaccine-related serious adverse experiences occurred in <0.1% of subjects. There was no safety signal with respect to allergic reactions or other immune-mediated diseases. The proportions of

[2] RECOMBIVAX HB is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

subjects reporting new medical conditions through up to 2.5 years Postdose 3 were comparable between subjects who received GARDASIL® and placebo subjects. Baseline HPV status did not impact vaccine safety. Use of GARDASIL® did not impact overall pregnancy outcomes. Administration of GARDASIL® to nursing mothers did not affect the health of the mother or the nursing child.

The proposed prescribing information for GARDASIL® includes the following indications:

GARDASIL® is a vaccine indicated for the prevention of cancer, precancerous or dysplastic lesions, genital warts, and infection caused by the HPV types targeted by the vaccine.

GARDASIL® is indicated for the prevention of the following caused by HPV 16 and HPV 18:

- cervical, vulvar, and vaginal cancer;
- cervical adenocarcinoma *in situ* (AIS);
- cervical intraepithelial neoplasia (CIN) grade 2 and grade 3;
- vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3; and
- vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3.

GARDASIL® is indicated for the prevention of the following caused by HPV 6, HPV 11, HPV 16, and HPV 18:

- cervical intraepithelial neoplasia (CIN) grade 1;
- genital warts (condyloma acuminata);
- VIN grade 1 and VaIN grade 1; and
- HPV infection.

Since the submission of the Original Application, additional safety data from Phase III trials have been obtained. These data were submitted in a Safety Update Report (SUR) on 03-Apr-2006. This briefing document presents cumulative safety data comprised of data presented in the Original Application and data from the SUR. This document is organized as follows:

Section 1 Introduction and Organization of the Document

Section 2 Background

Section 3 Clinical Efficacy

Section 4 Immunogenicity

Section 5 Clinical Safety

Tab E

EXHIBIT 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852-1448

JUN - 8 2006

Our STN: BL 125126/0

Merck & Co., Inc.
Attn: Dr. Patrick Brill-Edwards
Director
Worldwide Regulatory Affairs
Vaccines/Biologics
P.O. Box 4, BLB-22
West Point, PA 19486-0004

Dear Dr. Brill-Edwards:

We have approved your biologics license application (BLA) for Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine under your existing Department of Health and Human Services U.S. License No. 0002. Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine is indicated for vaccination in females 9 to 26 years of age for prevention of the following diseases caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18:

- Cervical cancer
- Genital warts (condyloma acuminata)

and the following precancerous or dysplastic lesions:

- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1.

Under this authorization, you are approved to manufacture Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine at Merck & Co., Inc., West Point, PA. The final formulation and filling is performed by Merck & Co., Inc., West Point, PA. Labeling and packaging will be performed by Merck & Co., Inc., West Point, PA. You may label your product with the proprietary name GARDASIL®. The vaccine will be supplied as a 0.5 mL single-dose vial, a carton of ten 0.5 mL single dose vials, a 0.5 mL single-dose prefilled syringe and a carton of six 0.5 mL single-dose prefilled syringes. The prefilled syringes will be preassembled with Ultra Safe® Passive™ Needle Guard devices.

The dating period for GARDASIL® vaccine shall be 36 months from the date of manufacture of the final filled container when stored at 2 to 8 °C. The 36 month shelf life includes all of the time that the final filled container is held at 2 to 8 °C prior to packaging. The date of manufacture shall be defined as the start date of filling into final containers. The monovalent bulk lots used to formulate the final container vaccine shall be held for no longer than 36 months at 2 to 8 °C.

Please submit final bulk samples and final container samples of the product together with lot release protocols in electronic format showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of GARDASIL® vaccine, or in the manufacturing facilities.

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring pediatric studies for GARDASIL® in girls less than 9 years of age and in boys and adolescent males less than 18 years of age.

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

We acknowledge the postmarketing clinical commitments outlined in your submission of June 6, 2006, as follows:

1. You have committed to conduct a short-term safety surveillance study in a U.S. Managed Care Organization (MCO). The study will include approximately 44,000 vaccinated subjects who will be followed for 60 days for assessment of general short-term safety (i.e., emergency room visits, hospitalizations, and deaths). The subjects will also be followed for 6 months subsequent to vaccination for new autoimmune disorders, rheumatologic conditions, or thyroiditis. Also, a sufficient number of children 11-12 years of age will be studied to permit an analysis of safety outcomes. The final study protocol will be submitted by December 31, 2006. Patient accrual will be completed by December 31, 2008. The study will be completed by June 30, 2009. The final study report will be submitted by September 30, 2009.

2. You have committed to collaborate with the cancer registries in four countries in the Nordic Region (Sweden, Norway, Iceland, and Denmark) to assess long-term outcomes following administration of GARDASIL®. In this study, approximately 5,500 subjects enrolled in Protocol 015 (one half from the placebo group that will have been vaccinated shortly after approval) will be followed for a total of 14 years. Two major goals of this study are: 1) to assess the long-term effectiveness of GARDASIL® by evaluating biopsy specimens for presence of HPV 6/11/16/18-related incident breakthrough cases of

CIN 2/3, AIS and cervical cancer, VIN 2/3 and vulvar cancer, and VaIN 2/3 and vaginal cancer; and 2) to assess whether administration of GARDASIL® will result in replacement of these diseases due to vaccine HPV types with diseases due to non-vaccine HPV types. This study is designed to accomplish these goals as discussed in the June 6, 2006, submission to your BLA. The final protocol for this study will be submitted by December 8, 2006. Patient accrual for this study was previously completed in the context of Protocol 015. This study will be completed by December 31, 2017, (14 years from initiation of the last patient enrolled in Protocol 015 in the four Nordic countries). The final study report will be submitted by December 31, 2018.

3. You have committed to conduct a study in collaboration with the Norwegian Government, if GARDASIL® is approved in the European Union and the Government of Norway incorporates HPV vaccination into its national guidelines, to assess the impact of HPV vaccination on the following in Norway:

   a. The long-term burden of HPV disease including the incidence of HPV 6/11/16/18-related cervical disease;
   b. The long-term burden of HPV disease caused by types other than HPV 6/11/16/18;
   c. The overall incidence of cervical HPV disease;
   d. The incidence of HPV-related cancers and pre-cancers (CIN 2/3, AIS and cervical cancer; VIN 2/3 and vulvar cancer; and VaIN 2/3 and vaginal cancer);
   e. The interaction between administration of GARDASIL® and pregnancy outcomes, especially congenital anomalies, by linking the vaccination registry with the Medical Birth Registry.

   The size and age range of the population studied will depend on the final vaccination guidelines implemented by the Norwegian Government. Although at this time no other governments in the Nordic region have committed to similar population studies, you will notify CBER of any other collaborations if they occur. The projected date of submission of the final study protocol is pending collaboration with the Norwegian Government as noted above. Patient accrual will be completed 6 years after study initiation. The study will be completed 7 years after study initiation. The final study report will be submitted 8 years after study initiation. In the event that approval of GARDASIL® does not occur in Norway, you will notify CBER and propose alternative approaches to obtain this information in a timely manner.

4. You have committed to submit final Clinical Study Reports (CSRs) for Protocols 013 and 015 when completed. As discussed, for these studies, an "all CIN 2/3, AIS or cervical cancer" analysis will evaluate the evidence for replacement of disease due to HPV types 16 and 18 with non-vaccine HPV types. Similar analyses will be done for VIN 2/3, VaIN 2/3, vulvar cancer and vaginal cancer. Protocol 013 was submitted in December 2001, and Protocol 015 was submitted in May 2002. Protocol 013 accrual was completed in March 2003, and Protocol 015 accrual was completed in May 2003. These analyses will be completed by April 30, 2007. The final reports for these studies (i.e., CSRs) to include the results of these analyses will be submitted by June 30, 2007.

5. You have committed to provide data concerning duration of immunity following administration of GARDASIL® as follows from the studies noted:

   a. The Nordic Long-Term Follow-up Study:
   Interim reports of effectiveness (i.e., incident breakthrough cases of CIN 2/3, AIS and cervical cancer; VIN 2/3 and vulvar cancer; and VaIN 2/3 and vaginal cancer) and immunogenicity results will be submitted in 2009, 2011, 2013, and 2015. The final study report will be submitted by December 31, 2018.

   b. Protocol 018 (Adolescent Sentinel Cohort):
   - Periodic reports beginning with Month 24 immunogenicity and long-term safety data will be submitted starting no later than March 30, 2007.
   - Publication of one year Post-dose 3 data will be submitted by January 30, 2007.
   - A Biologics License Supplement (BLS) for 1.5 year Post-dose 3 data will be submitted by June 30, 2007.
   - A Biologics License Supplement (BLS) for 2.5 year Post-dose 3 data will be submitted by December 31, 2007.
   - A Biologics License Supplement (BLS) for 5.5 year Post-dose 3 data will be submitted by December 31, 2010.

   c. Protocol 007:
   Publication of five-year immunogenicity data will be submitted by December 31, 2006.

   d. Protocol 005:
   Publication of seven and one half year immunogenicity data will be submitted by December 31, 2007.

6. You have agreed to establish a pregnancy registry in the U.S. to prospectively collect data on spontaneously-reported exposures to GARDASIL® during pregnancy. You have committed to submit a protocol for the U.S. pregnancy registry by July 20, 2006. You have agreed to address elements found in FDA's Guidance for Industry on Establishing Pregnancy Exposure Registries (9/2/2002) (http://www.fda.gov/cber/gdlns/pregexp.htm), as well as relevant Company Standard Operating Procedures. Furthermore, you have stated that you will notify CBER of significant deviations from this guidance and/or specify the deviations in the protocol. Patient accrual/data collection will begin at time of CBER's approval of the protocol and end five years later. You will submit annual reports and a final summary report of the U.S. pregnancy registry's findings five years after initiation of patient accrual/data collection. The U.S. pregnancy database will be considered completed one month after discontinuation of patient accrual for the purpose of preparing a five-year final summary report. The five-year final summary report will be submitted to CBER five years and six months after initiation of patient accrual/data collection. After reviewing the five-year data, Merck and CBER will meet to discuss the

need to continue further data collection in the U.S. pregnancy registry. CBER will have final approval regarding any decision to discontinue the U.S. pregnancy registry.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

We acknowledge the postmarketing clinical commitment outlined in your submission of June 6, 2006, as follows:

7. You have committed to provide CBER and simultaneously the FDA contractor for the Vaccine Adverse Events Reporting System (VAERS) all initial postmarketing "periodic" adverse experience reports received that are subject to periodic reporting (i.e., not covered under the "15-day Alert report" requirement under 21 CFR 600.80) on a monthly basis. Initial reports received by Merck in a given month will be submitted on VAERS forms to CBER and to the VAERS contractor by Working Day 10 of the following month. You have also agreed to provide, in accordance with 21 CFR 600.80, the Quarterly Periodic Adverse Experience Report to the VAERS contractor. The Quarterly Adverse Experience Report will contain a recapitulation of all initial reports submitted for the current reporting period and will include all follow up information on VAERS forms collected during that three-month period. You have committed to providing CBER this information using the aforementioned process, for the first three years after the date of licensure.

We acknowledge the postmarketing quality commitments outlined in your submission of June 2, 2006, as follows:

8. You have committed to submitting a proposal for establishing upper limits for the *in vitro* relative potency assay (IVRP) for HPV 6, 11, 16, and 18 for the Quadrivalent Final Container Product (QFCP). The upper quality control limits will be based on data obtained from full-scale manufacturing experience for the IVRP assay for each HPV type in the QFCP. The proposal will be submitted by July 31, 2006, and will also describe how lots with IVRP assay results that exceed these limits will be handled.

9. You have committed to providing stability data through the 48-month time point for the ongoing cell slurry stability study for HPV 6, 11, 16, and 18 by July 31, 2006.

10. You have committed to providing all currently available stability data for Monovalent Bulk Adsorbed Product (MBAP) Lots for HPV 6, 11, 16, and 18 to CBER by July 31, 2006. These MBAP lots are currently on full or abridged stability studies at 2 to 8 °C.

11. You have committed to providing the final study data for the HPV 6, 11, 16, and 18 MBAP lots on the accelerated stability study at 23 to 27 °C by July 31, 2006.

12. You have committed to providing all available stability data on all final container lots (both vials and syringes) currently on stability study to support the requested product shelf-life of 36 months at 2 to 8 °C by July 31, 2006. Additional updates to the stability

data for these lots will be submitted as they become available, through the study endpoint (42 months storage at 2 to 8 °C).

13. You have committed to providing all available stability data on all final container lots (both vials and syringes) used in the accelerated stability study at 23 to 27 °C by July 31, 2006. Additional updates to the stability data for these lots will be submitted as they become available, through the study endpoint (12 months storage at 23 to 27 °C).

14. You have committed to providing stability data from the sequential stability study. The stability data on the MBAP lots are covered by the commitment made in item 10 above as these lots were also used for the real time MBAP stability studies. Stability data on the QFCP lot formulated from MBAP lots stored at 2 to 8 °C for a minimum of 36 months will be submitted on an annual basis, at the time of the Annual Report submissions, through the completion of the study.

15. You have committed to providing study data for the first three full-scale lots filled into glass vials with Teflon-2 stoppers. Data from these final container stability studies will be submitted as they become available, through the study endpoint. However, we acknowledge that you currently do not have any plans to fill full-scale lots in glass vials with Teflon-2 stoppers.

16. You have committed to continue testing for Completeness of Adsorption (COA) on the QFCP until 50 full scale final container lots, representing 50 formulation lots, have been tested. You will submit COA data for these 50 lots to CBER as a CBE following licensure. CBER will evaluate the data and determine whether COA testing for lot release can be discontinued.

We request that you submit clinical protocols to your IND 9030, with a cross-reference letter to this biologics license application (BLA), STN BL 125126. We request that you submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 125126. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments, as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted), and

- an explanation of the status including, for clinical studies, the subject accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to FDA's Guidance for Industry: Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (February 2006) (see http://www.fda.gov/cber/gdlns/post130.htm) for further information.

Please submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and distribution reports as described in (21 CFR 600.81). Under 21 CFR 600.80(c) (2) [Periodic Adverse Experience Reports], you must report each adverse experience not reported under paragraph (c) (1) (i) of this section at quarterly intervals for the first 3 years following approval, and then at annual intervals. We note your clinical commitment in item 7 above to submit certain reports on a monthly basis for the first three years following approval. Since your product is characterized as a vaccine, submit these reports to the Vaccine Adverse Event Reporting System (VAERS) using the pre-addressed form VAERS-1.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling and implementation information on FDA Form 356h. Please provide a PDF-format electronic version of the label.

In addition, you may wish to submit two draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Two copies of final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253. All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have submitted data to support such claims to us and received CBER approval for such claims.

If you have any questions, please contact Dr. Gopa Raychaudhuri at 301-827-3070.

Sincerely yours,

Norman W. Baylor, Ph.D.
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research