3. **Executive Summary**

The sections of the BLA 125126 in support of clinical efficacy and safety of Gardasil have been reviewed. Additionally, a summary of these data were presented to the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) on May 18, 2006. The conclusions, which follow below, are derived from the review of the data submitted to the BLA and take into account the VRBPAC discussions regarding the proposed use of Gardasil.

The clinical data submitted to the BLA 125126 support the efficacy and safety of Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine (Gardasil) for the following indications:

- Cervical cancer, Cervical Intraepithelial Neoplasia (CIN) Grades 2/3, and Adenocarcinoma in situ (AIS) caused by the types contained within the vaccine (HPV 16, 18, 6, 11).
- Condyloma acuminata caused by types contained within the vaccine (HPV 6, 11, 16, 18).
- Vulvar Intraepithelial Neoplasia (VIN) grades 2/3, and Vaginal Intraepithelial Neoplasia (VaIN) grades 2/3 caused by types contained within the vaccine (HPV 6, 11, 16, 18).
- CIN 1 caused by types contained within the vaccine (HPV 6, 11, 16, 18).

The BLA also included data for consideration of the efficacy of Gardasil to prevent VaIN 1 and VIN 1 associated with HPV types HPV 16, 18, 6 and 11.

Efficacy

Efficacy was assessed in 4 placebo controlled, double blind, randomized Phase II and III clinical studies: Studies 005, 007, 013, and 015[1]. These studies enrolled females 16-23 (Studies 005, 007, and 013) or 16-26 (Study 015) years of age. In each of these studies efficacy was presented for the Per Protocol Efficacy Population (PPE) and several Modified Intent to Treat (MITT) Populations, including the MITT-3 population. The PPE population included subjects who had received all three doses within one year of enrollment, did not have major deviations from the study protocol and were naïve[2] (PCR and serology negative) for assessed vaccine serotypes at baseline and remained PCR negative through Month 7 (one month after dose 3). Efficacy was evaluated beginning one month after administration of the third dose. The MITT-3 population included subjects naïve and non-naïve[3] (PCR and/or serology positive for one or more vaccine serotypes) at baseline, and efficacy was evaluated beginning one month post the first dose of the vaccine. The MITT-3 population may be considered to approximate the general population of women who are HPV naïve and HPV non-naïve, some of whom have HPV related disease at baseline.

[1] Study 005 used the monovalent vaccine type HPV 16. Studies 007, 013, and 015 used Gardasil, except 304 subjects in Protocol 013 who received monovalent HPV 16 as part of a bridging study.
[2] Naïve = seronegative and PCR negative (cervicovaginal [CV] sample) for the relevant HPV type
[3] Non-naïve = seropositive and/or PCR positive (cervicovaginal [CV] sample) for the relevant HPV type

HPV 16/18 related cervical cancer, Cervical Intraepithelial Neoplasia (CIN) grades 2/3, Adenocarcinoma in situ (AIS), or Worse

In November 2001, the Vaccines and Related Biological Products Advisory Committee considered appropriate endoints for licensure of HPV vaccines and determined that given standard of care in developed countries, CIN 2/3 and AIS or worse could be considered a valid surrogate endpoint for cervical cancer. Thus, the primary efficacy endpoint for Study 015 and the combined studies was histopathological diagnosis of CIN 2/3, AIS or worse, with evidence of HPV 16 or 18 in the specimen. Study 015 and the combined studies, analyses showed Gardasil was efficacious in preventing HPV 16- or 18- related CIN 2/3 or AIS in the PPE population (Table 1). When efficacy was evaluated in cases counted one month following the first dose in the MITT-3, which included women who were HPV-naïve and non-naïve to the relevant types, the estimate of efficacy decreased to approximately 39% (MITT-3 population, Table 1).

TABLE 1
Efficacy of Gardasil to Prevent HPV 16- or 18 Related CIN 2/3, AIS, or Worse (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 16, 18 related CIN 2/3, AIS, or Worse	015	PPE	100% (75.8, 100%)
	005, 007, 013, 015	PPE	100% (92.9, 100%)
	015	MITT-3	39.2% (16.9, 55.8%)
	005, 007, 013, 015	MITT-3	39.0% (23.3, 51.7%)

HPV 6-, 11-, 16-, or 18 related Cervical Intraepithelial Neoplasia (CIN) grades 2/3, Adenocarcinoma in situ (AIS), or Worse

When efficacy evaluation was expanded to include CIN 2/3, AIS or worse, with evidence of HPV 6, 11, 16, or 18 in the specimen, i.e., all HPV types included within Gardasil, the point estimate of efficacy was 100% for the PPE population of either Study 015 alone or the combined studies (Table 2). In the efficacy analyses with the MITT-3 population (regardless of baseline vaccine HPV type status) the point estimates of efficacy were 36-41%, lower than demonstrated in the PPE population. Among cases of CIN 2/3 or AIS caused by HPV 6, 11, 16, or 18 in the MITT-3 population, 79% occurred in subjects who had an abnormal Pap test at day 1 and/or who were PCR and/or seropositive for the relevant type at day 1.

TABLE 2
Efficacy of Gardasil to Prevent HPV 6-, 11-, 16- or 18 Related CIN 2/3, AIS, or Worse (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 6, 11, 16, 18 related CIN 2/3, AIS, or Worse	015	PPE	100% (81.8, 100%)
	005, 007, 013, 015	PPE	100% (91.0, 100%)
	015	MITT-3	40.9% (19.7, 56.9%)
	005, 007, 013, 015	MITT-3	36.3% (19.4, 49.9%)

HPV 6-, 11-, 16-, or 18 related Condyloma Acuminata
Data to support the prevention of HPV 6, 11, 16, or 18 related condyloma acuminata come from the primary analysis of the PPE population of Study 013 and the analysis of the combined PPE populations in Studies 007, 013, and 015. These analyses demonstrated efficacy of Gardasil to prevent HPV 6, 11, 16, and/or 18 related condyloma acuminata (Table 3). When the population was expanded to include non-naïve subjects (MITT-3 population), vaccine efficacy in Study 013 was 69.5% [95% CI: 48.9, 82.5%] and in the combined analysis 68.5% [95% CI: 57.5, 77.0%].

TABLE 3
Efficacy of Gardasil to Prevent HPV 6-, 11-, 16- or 18 Related Condyloma Acuminata (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 6, 11, 16, 18 related Condyloma Acuminata	013	PPE	100% (86.4, 100%)
	007, 013, 015	PPE	98.9% (92.3, 100%)
	013	MITT-3	69.5% (48.9, 82.5%)
	007, 013, 015	MITT-3	68.5% (57.5, 77.0%)

HPV 6-, 11-, 16-, or 18 related Vulvar Intraepithelial Neoplasia (VIN) Grades 2/3 or Vaginal Intraepithelial Neoplasia (VaIN) Grades 2/3
A co-primary endpoint for Study 013, included in the composite endpoint "External Genital Lesions," was diagnosis of VIN 2/3 and VaIN 2/3 with evidence of HPV 6, 11, 16, or 18 in the specimen. Data to support this indication also come from an analysis of combined data from Studies 007, 013, and 015. In Study 013 the efficacy of Gardasil against HPV related 6, 11, 16, and/or 18 related VIN 2/3 or VaIN 2/3 was 100% [95%: 30.2, 100%] for the PPE population. In the analysis of combined studies data, analysis of efficacy was 100% [95% CI: 67.2, 100%]. When the 013 or combined studies analyses populations were expanded to include non-naïve subjects (MIIT-3 population) the point estimates of efficacy decreased (Table 4).

Analysis of the ability of Gardasil to prevent 6, 11, 16, and/or 18 related VIN 2/3 was provided for the combined studies. In the PPE population efficacy of Gardasil was 100% [95% CI: 41.4, 100%], and when the population include non-naïve subjects (MITT-3 population), efficacy was 68.1% [95% CI: 22.7, 89.4%] (Table 4).

The ability of Gardasil to prevent HPV 6, 11, 16, and/or 18 related VaIN 2/3 was presented for the combined Studies 007, 013, and 015. Although the point estimates for efficacy were 100% and 78% for the PPE and MITT-3 populations, respectively, the number of VaIN 2/3 cases was small and therefore the lower bound of the 95% CI for both estimates was less than zero. (Table 4).

TABLE 4
Efficacy of Gardasil to Prevent HPV 6-, 11-, 16- or 18 Related Vulvar Intraepithelial Neoplasia (VIN) Grades 2/3 and Vaginal Intraepithelial Neoplasia (VaIN) Grades 2/3 (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 6, 11, 16, 18 Related VIN Grades 2/3 or VaIN Grades 2/3	013	PPE	100% (30.2, 100%)
	007, 013, 015	PPE	100% (67.2, 100%)
	013	MITT-3	63.7% (<0.0, 91.6%)
	007, 013, 015	MITT-3	73.3% (40.3, 89.4%)
HPV 6, 11, 16, 18 Related VIN Grades 2/3	007, 013, 015	PPE	100% (41.4, 100%)
	007, 013, 015	MITT-3	68.1% (22.7, 88.5%)
HPV 6, 11, 16, 18 Related VaIN Grades 2/3	007, 013, 015	PPE	100% (<0.0, 100%)
	007, 013, 015	MITT-3	77.7% (<0.0, 97.7%)

HPV 6, 11, 16, and/or 18 Related Cervical Intraepithelial Neoplasia (CIN) Grade 1
Efficacy against HPV 6, 11, 16, 18 related CIN 1 is supported by analyses from Study 013 and combined Studies 007, 013, and 015. The Study 013 and combined study analyses showed Gardasil was efficacious in preventing HPV 6, 11, 16, 18 related CIN 1 (Table 5). When the MITT-3 population was assessed, efficacy in Study 013 was 51.0% [95% CI: 21.9, 58.6%], and in the combined studies population efficacy of Gardasil was 54.4% [95% CI: 27.9, 86.1%].

TABLE 5
Efficacy of Gardasil to Prevent HPV 6-, 11-, 16- or 18 Related Cervical Intraepithelial Neoplasia (CIN) Grade 1 (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 6, 11, 16, 18 related CIN 1	013	PPE	100% (84.1, 100%)
	007, 013, 015	PPE	93.1% (81.4, 98.2%)
	013	MITT-3	51.0% (27.0, 67.1%)
	007, 013, 015	MITT-3	54.4% (41.8, 64.5%)

Additional Endpoints Evaluated
HPV 6, 11, 16, and/or 18 Related VIN 1 and VaIN 1
Although the clinical relevance of VIN 1 and VaIN 1 is not well defined, the sponsor provided an assessment of vaccine efficacy against HPV 6, 11, 16, 18 related VIN 1 and HPV 6, 11, 16, 18 related VaIN 1 for Study 013 and combined studies 007, 013, and 015. These data are shown in Table 6. In the PPE population of Study 013, efficacy against HPV 6, 11, 16, 18 related VIN 1 was 100% [95% CI: <0.0, 100%], and in the PPE population of the combined studies 100% [95% CI: 55.4, 100%]. In the MITT-3 population of Study 013, vaccine efficacy against VIN 1 was 16.8% [95% CI: <0.0, 79.9%]. In the combined studies MITT-3 population, efficacy against this endpoint was 57.8% [95% CI: <0.0, 84.0%].

In Study 013, efficacy against HPV 6, 11, 16, 18 related VaIN 1 in the PPE population was 100% [95% CI: <0.0, 100%]. In the combined studies PPE population, efficacy was 100% [95% CI: 30.6, 100%]. In the MITT-3 population of Study 013, efficacy against HPV 6, 11, 16, 18 related VaIN 1 was 88.9% [95% CI: 20.0, 99.7%]. In the combined studies analyses, efficacy in the MITT-3 population was 76.4% [95% CI: 27.7, 94.2%].

TABLE 6
Efficacy of Gardasil to Prevent HPV 6-, 11-, 16- and/or 18 Related Vulvar Intraepithelial Neoplasia (VIN) Grade 1 and Vaginal Intraepithelial Neoplasia (VaIN) Grade 1 (PPE and MITT-3 Populations)

Endpoint	Study	Population	Estimate of efficacy (95% CI)
HPV 6, 11, 16, 18 related VIN Grade 1	013	PPE	100% (<0.0, 100%)
	007, 013, 015	PPE	100% (41.9, 100%)
	013	MITT-3	16.8% (<0.0, 79.9%)
	007, 013, 015	MITT-3	57.8% (<0.0, 84.0%)
HPV 6, 11, 16, 18 related VaIN Grade 1	013	PPE	100% (<0.0, 100%)
	007, 013, 015	PPE	100% (30.6, 100%)
	013	MITT-3	88.9% (20.0, 99.7%)
	007, 013, 015	MITT-3	76.4% (27.7, 94.2%)

Efficacy Bridge to Females 9-15 years of age

Vaccine efficacy (with histology-confirmed endpoints as described above) was assessed in female subjects 16-26 years of age. Analyses of naïve subjects (PPE population) have higher estimates of efficacy than analyses which also included non-naïve subjects (MITT-3 population). Furthermore, efficacy analyses of non-naïve subjects (seropositive and/or PCR positive at baseline) as compared to naïve subjects for HPV 6, 11, 16, 18 related CIN 2/3, AIS or worse and for HPV 16/18 related CIN 2/3, AIS or worse suggest that Gardasil has limited efficacy in non-naïve subjects. (See discussion in Overall Efficacy Section Efficacy and Tables 275 and 276). Thus, subjects who have not been exposed to HPV serotypes covered by the vaccine, among them younger girls, may benefit from being vaccinated prior to HPV exposure. A serology bridging study, 016, was conducted to compare the immune response of females 10-15 years of age administered Gardasil to that of females 16-23 years of age administered Gardasil. The study demonstrated that following three doses of Gardasil, the GMT and seroresponse rate of females 10-15 years of age was non-inferior to those of females 16-23 years of age.

In addition, the sponsor compared the immune response of females 9-15 years of age (participating in studies 016 and 018) following three doses of Gardasil to the response of females 16-26 years of age who participated in efficacy studies 013 and 015. The sponsor demonstrated that one month following the third dose of Gardasil, the HPV 6, 11, 16, and 18 GMTs of girls 9-15 years of age were non-inferior to those of females 16-26 years of age who participated in the efficacy studies (013 and 015).

Duration of Efficacy
Duration of efficacy has not yet been determined. It is not known whether booster doses will be needed. See post-marketing commitments at the end of the executive summary.

No immune correlate of protection was identified from the Phase III trials. Following three doses of Gardasil at Month 7, the rate of seroconversion was > 99% for all vaccine HPV types in all age groups evaluated. In addition, following three doses of Gardasil, the GMT for each of the vaccine HPV types were higher than those of placebo subjects positive for one or more of the vaccine types at baseline. The duration of immune response has not been determined. However, at 24 months following dose 1, the GMT to each of the vaccine HPV types were at or above the levels seen in unvaccinated subjects with serological evidence of HPV infection to a vaccine type at baseline. The manufacturer has committed to following for long term efficacy and immune response. See post-marketing commitments at the end of the executive summary.

Safety:
In the BLA submission, 11792 subjects had received at least 1 dose of Gardasil in the 5 clinical studies (007, 013, 015, 016, and 018). The majority of these subjects, (10721) were female, and of these, 3422 were females 9-17 years of age who received at least 1 dose of Gardasil. An additional 2146 subjects received at least one dose of the monovalent vaccine in 5 studies (001, 002, 004, 005, and 006).

Table 7
Subjects Administered at least one dose of monovalent HPV vaccine, Gardasil, or placebo in clinical studies in the BLA

Study	Monovalent Vaccine N=2146	Gardasil N=11792	Placebo N=11004
001	112		28(a)
002	82		27(a)
004	428		52(a)
005	1193		1198(a)
006	27		13(b)
007		289	292(c)
013	304	2717	2725(a)
015		6082	6075(a)
016		1525	0
018		1179	594(d)
TOTAL	2146	11792	11004

(a)Placebo = --- mcg alum as amorphous aluminum hydroxide sulfate AAHS
(b) Placebo = --- mcg alum as AAHS
(c) Placebo = 146 subjects with --- mcg AAHS and 146 subjects with --- mcg AAHS
(d) Placebo = saline placebo
Source: Table 2.7.4:2, p. 62 and Table 2.7.4:3, p. 65, Summary of Clinical Safety, original BLA submission

Injection Site Reactions: In 4 placebo controlled trials in which solicited local and systemic events were monitored using Vaccine Report Cards, a higher proportion of Gardasil recipients experienced local injection site reactions (app. 83%) within the 5 days after any dose, as compared to aluminum adjuvant placebo recipients (77%) or saline

placebo recipients (50%). The majority of injection site adverse events were mild to moderate in severity. The most common local reactions included pain, swelling, and redness.

Systemic Reactions: In studies in which solicited local and systemic adverse events were monitored using Vaccine Report Cards, the proportion of subjects with a systemic adverse event within 15 days after any dose was comparable between the Gardasil recipients (59%) and combined placebo recipients (60%). In study 018, the rates of systemic adverse events were assessed following administration of Gardsil or saline placebo, and the rates of systemic adverse events were lower than observed in other studies but comparable between study groups. Overall, the most common systemic adverse events in both Gardasil and placebo recipients included headache, pyrexia (most low-grade), and nausea.

Discontinuations due to Adverse Events: Few subjects in the Gardasil group (0.18%) and the placebo group (0.15%) discontinued from the trials because of an adverse event. The majority of discontinuations were due to deaths (most after traffic accidents and serious adverse events without apparent association to the vaccine). Please see below and safety summary for details.

Serious Adverse Events: In comparative studies, there were a comparable number of serious adverse events throughout the study in Gardasil recipients (136) or placebo group (125). A comparable **number of subjects** administered Gardasil or placebo reported a Serious Adverse Event (Gardasil N=102, 0.9%; placebo N=99 (1.0%). As of the safety update report of 3/8/06, 59/11778 (0.5%) of Gardasil recipients had experienced an SAE within 15 days after vaccination, and 43 placebo recipients (0.4%) had experienced an SAE within that time frame.

Deaths: In comparative studies, there were 10 deaths among subjects who received Gardasil (0.08%) and 7 (0.07%) among subjects who received placebo. The most common cause of death was motor vehicle accident (4 Gardasil, 3 placebo), followed by suicide/overdose (1 Gardasil, 2 placebo), and pulmonary embolism/DVT (1 Gardasil and 1 placebo). In addition, in the Gardasil group, there were 2 cases of sepsis [1 subject at 395 days following dose 3 and 1 subject at 625 days postdose 3], 1 case of pancreatic cancer (578 days following dose 3), and 1 case of arrhythmia (27 days postdose 1 in a young male with a family history of arrhythmia). In the placebo group, there was 1 case of asphyxia. There was no apparent pattern identified among these events.

Additionally, in Study 005, there was one death in each of the treatment groups: in the HPV 16 vaccine group, there was death in a plane crash 3 years following dose 3 and in the placebo group, there was one suicide 2 years following dose 3.

New Medical Conditions: The number and percentage of new medical conditions reported to occur within the 7 month vaccination period and in the post-seven month vaccination period among subjects who received Gardasil or placebo in comparative studies was reviewed. The incidence rates during the vaccination period in both

treatment groups (49.5% among Gardasil recipients and 49.0% of placebo recipients) were similar. The incidence rates in the post-vaccination period (49.5% among Gardasil recipients and 52.0% among placebo recipients) were also similar.

Pregnancy Outcomes: Overall, pregnancy outcomes among subjects who received Gardasil or placebo in comparative studies were similar: a comparable proportion of pregnancies with live births (Gardasil, 62% and placebo, 60%) and spontaneous abortions (app. 25% in each group) was noted. A similar pattern of adverse events and occurrence in pregnant subjects were noted in the Gardasil group (N=40, 4.2%) and placebo group (N=41, 4.3%). The events in each treatment group were related to conditions leading to C-section, premature labor, and conditions associated with pregnancy, such as pre-eclampsia. For a discussion of congenital anomalies and lactation, see Section 10.3.6.

Additional Indications requested by sponsor
Use in Males: The sponsor had proposed that Gardasil be indicated for use in all adolescents 9-17 years of age, including males. The BLA included safety and immunogenicity data from Studies 016 and 018 in which approximately 1000 males 9-15 years of age were administered a three dose series of Gardasil. No safety or immunogenicity data in males > 15 years was presented in the BLA. A study of efficacy of Gardasil to prevent HPV 6, 11, 16, 18 infection or disease in males 16-23 years of age is underway, and it is anticipated that results will be available in 2008. These results, together with safety data and a serological bridge to younger males (9-15 years of age) will be submitted as a supplement to the Gardasil license to support an indication in males.

Prevention of Vulvar and Vaginal Cancer: It is likely that VIN 2/3 and VaIN 2/3 associated with HPV are precursors to vulvar cancer (especially those which occur in younger women) and most cases of vaginal cancer. The data from the trials demonstrate a favorable impact on the incidence rate of VIN 2/3 and VaIN 2/3 associated with HPV 6, 11, 16, and/or 18. It is expected that with the final closeout of Protocols 013 and 015, there will be additional cases of VIN 2/3 and VaIN 2/3 related to the vaccine types (predominantly HPV 16 and 18). Thus, with additional cases and further consideration of the literature, an indication for the prevention of vulvar and vaginal cancers based on the prevention of VIN 2/3 and VaIN 2/3 may be reconsidered.

Prevention of HPV 6, 11, 16, 18 infection: CBER did not concur with the indication of prevention of HPV 6, 11, 16, and/or 18 infection since almost all preventive infectious disease vaccines are indicated for the prevention of disease caused by the infectious agent.

Issues identified during the clinical review
HPV related disease occurred in Gardasil recipients.
Some non-naïve subjects (sero- and/or PCR positive for one or more vaccine HPV types at baseline) developed HPV disease related to that HPV type(s) or to HPV types not included in Gardasil. Some vaccine recipients who were naïve (i.e., seronegative and PCR negative at baseline) to all four vaccine HPV types developed disease related to an

HPV type not included in the vaccine (although these had not been identified by type specific PCR at the time of the BLA submission). The sponsor has indicated that results of type specific HPV identification for non-vaccine HPV types will be available in spring 2007. In review of the combined datasets (studies 007, 013, and 015), there were an approximately equal number of diagnoses of CIN 3 in naïve Gardasil recipients (40) and naïve placebo recipients (39) in which the HPV type was not confirmed as vaccine related by PCR.

HPV related disease in non-naïve subjects
An exploratory subgroup analyses for study 013 suggested a concern that subjects administered Gardasil who were seropositive and PCR positive for the vaccine relevant HPV types had a greater number of CIN 2/3 or worse cases as compared to such subjects administered placebo. Review of the potential imbalances in baseline characteristics of this subgroup revealed that a higher percentage of these subjects administered Gardasil had High Grade Intraepithelial Lesion (HSIL) on Pap test at baseline [6.5%] as compared to placebo recipients in this subgroup [3.7%]. In addition, a slightly higher proportion of Gardasil recipients in this subgroup [35.9%] had a history of prior cervicovaginal infection as compared to the placebo recipients [32.1%].

A similar exploratory subgroup analysis for Study 015 did not raise a concern for enhancement of cervical disease due to HPV disease. In a combined analysis of Studies 013 and 015, the sponsor presented data to show that of 554 Gardasil subjects who were seropositive and PCR positive at baseline, 5.0% had HSIL at baseline compared to 3.7% of placebo recipients. Despite some difficulties in interpreting subgroup data, the sponsor provided an analysis of the probability of developing a case of HPV 6, 11, 16, 18 related CIN 2 or worse, which was modeled as a function of the following characteristics: smoking status, region, age, lifetime number of sexual partners, number of new sexual partners in the 6 months prior to study start, Pap test diagnosis, using logistic regression. The vaccine group was also included in the model. In the logistic regression modeling for the Combined dataset of Efficacy Studies (Studies 007, 013, and 015), the only variable that was nominally statistically significant was Day 1 Pap test results ($p<0.001$). It is difficult to draw conclusions based on this subgroup analysis. Further surveillance of this subgroup will be included in the post-marketing studies (see below). (Source: Efficacy Information Amendment, Regression Analysis, 6/1/06).

Based on these data, CBER concluded that there was no clear evidence of vaccine related disease enhancement. There is no evidence of therapeutic effect of the vaccine, especially in those PCR positive and seropositive for the relevant HPV type.

Pregnancy Outcomes
Among women who conceived within 30 days of vaccination, there were 5 cases of congenital anomalies in infants born to mothers who received Gardasil and none in infants born to mothers in the placebo group. The five diverse anomalies included the following: hip dysplasia, ankyloglossia with pyloric stenosis, congenital hydronephrosis, congenital megacolon, and club foot. As of 1/25/06, there were 17 congenital anomalies in infants born to Gardasil recipients and 19 to placebo recipients. The pattern of

anomalies does not suggest an association with the vaccine. Pregnancies that occurred in Studies 013 and 015 that had not been completed at the time of the BLA submission will be followed to completion for the close out reports. In addition, a pregnancy registry study is planned as a post-marketing commitment to continue follow-up of pregnancy outcomes. The vaccine is not recommended for use in women known to be pregnant.

Respiratory illnesses and gastroenteritis in the infants whose mothers received Gardasil while breastfeeding

There was a higher proportion of cases of respiratory illnesses and gastroenteritis among infants of mothers who were administered Gardasil during the time they were breastfeeding their infants. Specifically, there were 12 cases of respiratory illnesses in the Gardasil group and 6 in the placebo group (6 within 30 days of vaccination in the Gardasil group and 2 in the placebo group), and 5 cases of gastroenteritis in the Gardasil group as compared to 2 in the placebo group (all cases in the Gardasil group were > 30 days after vaccination). One case in the vaccine group occurred in an infant with anomalous pulmonary venous malformation which is often associated with respiratory distress and chest infections.[4] All cases of respiratory events in both groups who were breastfeeding their infants occurred in the Latin American region. The sponsor noted that most of the subjects who carried a baby to term and breastfed were from this region. Most of these subjects received further doses of the vaccine without an additional respiratory event occurring in these infants. The number of events was small and the times to event post vaccination were variable for these events, and definitive associations could not be made. In infants of mothers who were potentially exposed to study material (and whose mothers were <u>not</u> breastfeeding), there were 13 infants with respiratory events in the placebo group (including 5 infants with neonatal respiratory distress syndrome) compared to 14 infants in the Gardasil group (including 2 infants of neonatal respiratory distress syndrome) in the neonatal period and post-neonatal period. Overall there were 26 respratory events in infants whose mothers received Gardasil, and 19 respiratory events in infants whose mothers received placebo. The package insert will include a cautionary statement about use of Gardasil in women who are breastfeeding their infants. Please see Safety Overview for data presentation and full discussion.

The Vaccines and Related Biological Products Advisory Committeee (VRBPAC) meeting

On May 18, 2006 following presentations by the manufacturer and FDA, the VRBPAC voted unanimously that the data supported the efficacy of Gardasil to prevent HPV 16/18 related cervical cancer, cervical AIS, CIN 2/3 or worse; HPV 6/11/16/18 related VIN 2/3 amd VaIN 2/3; and HPV 6/11/16/18 related condyloma acuminata. After further discussion with the sponsor, HPV 6/11/16/18 related CIN 1 was also added to the indications. The following items and recommendations were also discussed during the meeting:

1. Several members of the Advisory Committee stated that the vaccine would be efficacious in subjects who are naïve for the relevant vaccine HPV type. However, it was acknowledged that type-specific pre-vaccination screening would not be feasible. Therefore, presentation of data showing an apparent lack of efficacy against vaccine HPV types for which a woman is PCR positive and/or

[4] Corbett HJ and Humphrey GM. Pulmonary sequestration. Paediatr Respir Rev. 2004 mar; 5(1): 59-68.

seropositive prior to vaccination was important information. Thus, the package insert should include information from all subjects regardless of baseline HPV status (i.e., the MITT-3 population)

2. Several members of the Advisory Committee emphasized that use of the vaccine does not affect the need for continued Pap test screening as per standard of care. A recommendation was made that a statement regarding this issue should be included in the label.
3. Recommendations were made to assess duration of the immune response and efficacy and assess the need for booster dosing as time progresses.
4. Replacement disease due to HPV types not included in the vaccine should be assessed following licensure.

Post-marketing commitments (See FDA approval letter for final wording of Post-Marketing commitments):

1. Short Term Safety Surveillance: Merck will conduct a short term safety surveillance study of 44,000 vaccinated subjects in a U.S. Managed Care Organization (MCO). Subjects will be followed for 60 days for assessment of general short-term safety (emergency room visits, hospitalizations, and deaths). The subjects will also be followed for 6 months following the third dose for new autoimmune disorders, rheumatologic conditions, or thyroiditis adverse events, and will include ascertainment of new autoimmune disorders, rheumatologic conditions, or thyroiditis. The population will include a sufficient number of children 11-12 years old to permit an analysis of safety outcomes.

2. Pregnancy Registries: Merck will establish a pregnancy registry in the U.S. to prospectively collect data on spontaneously-reported exposures to GARDASIL during pregnancy. The U.S. registry will address elements found in CBER's "Guidance for Industry: Establishing Pregnancy Exposure Registries (9/20/2002)."

3. Nordic Long-Term Follow-up Study: Merck is collaborating with four countries in the Nordic Region (Sweden, Norway, Iceland, and Denmark) to assess long-term outcomes following administration of GARDASIL in approximately 5,500 subjects enrolled in Protocol 015 (one half from the placebo group that will be vaccinated shortly after licensure) for a total of 14 years. This study will assess the long-term effectiveness of the vaccine by detecting HPV 6/11/16/18 related cervical disease including CIN 2/3, AIS, and cervical cancer,VIN 2/3, VaIN 2/3 and vaginal and vulvar cancer due to waning immunity, and assess any replacement with non-vaccine types.

4. Norway Population Study: Provided that GARDASIL is approved in the European Union, the Government of Norway intends to incorporate HPV vaccination into its National Guidelines (Norwegian equivalent of the ACIP). Merck will collaborate with the Norwegian Government to assess the impact of HPV vaccination on: 1) the long-term burden of HPV disease including the incidence of HPV 6/11/16/18-related cervical disease, the incidence of HPV disease caused by types other than HPV 611 1/16/18, the overall incidence of cervical HPV disease, and incidence of HPV-related cancers, pre-cancers (CIN 2/3, AIS and cervical cancer; VIN 2/3 and vulvar cancer; and VaIN 2/3 and

vaginal cancer) and 2) the interaction between administration of GARDASIL and pregnancy outcomes, especially congenital anomalies, by linking the vaccination registry with the Medical Birth Registry.

5. Final Clinical Study Reports (CSRs) for Protocols 013 and 015: Merck intends to submit completed CSRs when these two Protocols are completed. For Protocols 013 and 015, an end-of-study analysis for "all CIN 2/3, AIS or worse" analysis will evaluate the evidence for replacement of disease due to HPV types 16 and 18 with non-vaccine types (estimated completion spring of 2007). The sponsor will also evaluate all VIN 2/3 and vulvar cancer cases and VaIN 2/3 and vaginal cancer cases in the final analyses.

6. Frequency of Clinical Safety Reporting: Merck agrees to simultaneously provide CBER and the FDA contractor for Vaccine Adverse Events Reporting System (VAERS) all initial post marketing "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. Merck also commits to provide the Quarterly Periodic Adverse Experience Report to the VAERS contractor. This 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. Merck commits to providing CBER this information using the aforementioned process, for the first three years after the date of licensure.

7. Duration of Immunity: Merck plans to provide evidence of duration of immunity following administration of GARDASIL, by targeting the following: (i) submission of periodic reports of effectiveness and immunogenicity results from the Nordic Long-Term Follow-up Study to regulators beginning in 4Q 2008, (ii) submission of periodic reports for Protocol 018 (Adolescent Sentinel Cohort), beginning with Month 24 imrnunogenicity and long-term safety data at time of filing in 1Q 2007, (iii) publication of five year immunogenicity data from Protocol 007 in late 2006, and (iv) publication of seven and one half year immunogenicity data from Protocol 005 in 2007.