Summary Basis for Regulatory Action

Date: August 25, 2010

From: Jeff Roberts, M.D., Chair of the Review Committee

BLA/ STN#: 125126/773

Applicant Name: Merck & Co.

Date of Submission: January 17, 2008

PDUFA Goal Date: April 6, 2011

Proprietary Name/ Established Name: GARDASIL®

Additional Indication Sought Under This BLA Supplement: The applicant sought to extend all of Gardasil's current indications for females 9 to 26 years of age to females 27 to 45 years of age.

Recommended Action: Approval is not recommended for extension of the current indications for Gardasil to females 27 to 45 years of age. However, approval of the BLA supplement is recommended for revision of the package insert to display a limited set of data from the clinical study in women 27 to 45 years of age.

Signatory Authorities Action: Approval of recommended action.

Offices Signatory Authority:

Wellington Sun, M.D.
Director, Division of Vaccines and Related Products Applications
Office of Vaccine Research and Review

√ I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

Table 1: Review documents used in compiling this SBRA:

Review Category	Reviewer
Clinical Review	Jeff Roberts, M.D.
Statistical Review	Martha Lee, Ph.D.
Labeling Review	Lisa Stockbridge, Ph.D.
Bioresearch Monitoring Review	Solomon Yimam

1. Introduction

GARDASIL® is a non-infectious recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. It was licensed in the U.S. in June of 2006. With regard to females, the vaccine is currently indicated for ages 9 to 26 years for the prevention of:

- Cervical, vulvar, and vaginal cancer caused by HPV types 16 and 18
- Associated precursor dysplastic lesions (CIN, VIN, VaIN, AIS) caused by HPV types 6, 11, 16, and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

In January of 2008, Merck submitted Biologics License Application supplement (sBLA) 125126/773, to expand the usage of GARDASIL® to include females 27 to 45 years of age.

2. Background

Human papillomavirus (HPV) infection initially occurs in the teens and early 20's, in conjunction with the initiation of sexual activity. Among the oncogenic high risk (hrHPV) infections that persist and progress, a few will go on to cause cancer years to decades later, which explains the peak in the 5^{th} to 6^{th} decade of life in the incidence of invasive cervical cancer.

Early in the clinical development program, the applicant conducted a series of studies in young adult women that demonstrated very consistent and robust efficacy of Gardasil in the prevention of HPV-associated infection and advanced cervical dysplasia. To evaluate the efficacy of Gardasil in mid-adult women, aged 27 to 45 years, the applicant has completed a trial in ~3800 women randomized 1:1 to receive Gardasil or placebo control, in which the primary endpoint was a composite of persistent HPV infection, any grade of cervical dysplasia, and any dysplastic or condylomatous external genital lesion.

The mechanism by which the licensed HPV vaccines prevent advanced dysplasia and cancer is thought to be through prevention of initial infection with hrHPV. However, with increasing age, an increasing percentage of the HPV detected in women represents prevalent, not newly acquired infection. In addition, although the rate of acquisition of apparent new infections is still substantial among older women, it remains unclear what percentage of these events represent a *bona fide* initial infection versus reactivation of a latent, previously undetectable infection. Finally, it has not yet been definitively demonstrated that newly detected infections in older women progress to cervical cancer with the same frequency as those occurring in younger women. CBER's assessment of

the recent data addressing these issues is that they do no tend to strengthen the validity of persistent infection as the appropriate endpoint for evaluating efficacy in older women.

Therefore, weighing all the evidence, CBER concluded that the advanced disease endpoint of CIN2+ is an important efficacy benchmark to consider in older women, perhaps even more so than in younger women. Although CBER recognizes that the study submitted to the sBLA was not powered for an advanced disease endpoint, the insubstantial efficacy and/or lack of statistical significance for CIN2+ apparent in every analysis of the data does not support a conclusion that Gardasil is generally effective in the age group (27 to 45 years of age) studied in the pivotal trial.

CBER expressed these and other concerns (including that efficacy on the primary endpoint was driven largely by persistent infection) in two complete response (CR) letters. In both cases, CBER concluded that the applicant's response did not adequately address the issues raised. Subsequently, CBER planned to discuss the data with a panel of experts at a Vaccines and Related Biological Products Advisory Committee (VRBPAC). However, the applicant withdrew the request to expand the usage of Gardasil to mid-adult women and chose to make less substantial revisions to the package insert to display limited data from the submitted study.

3. Chemistry Manufacturing and Controls (CMC)

Full CMC review of the product was completed at the time Gardasil was originally licensed in June 2006. All lots of vaccine used in the studies in mid-adult women were reviewed and released for distribution by CBER.

In addition, the laboratory assays to document HPV infection by PCR and to measure immune response to vaccination (competitive Luminex Immunoassay (cLIA)) have been reviewed by CBER. Therefore, no new CMC review was performed in the context of this submission.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were requested or submitted in the context of this submission.

5. Clinical

Clinical data from a single study (019) were submitted to the sBLA in support of the proposed expansion of the indication. In addition to data from Study 019, the clinical reviewer re-analyzed relevant data from studies in young adult women, including from Studies 013 and 015.

Efficacy

Study 019 was a randomized, double-blind, placebo-controlled, multicenter trial, in which ~3800 women 24-45 years of age were randomized 1:1 to receive Gardasil or amorphous aluminum hydroxyphosphate sulfate (AAHS) control. The primary efficacy objective was:

"to demonstrate that administration of Gardasil reduces the combined incidence of HPV 6/11/16/18-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, cervical dysplasia (any grade CIN), AIS, and cervical cancer, compared with placebo in women 24 to 45 years of age who are naïve to the relevant HPV type."

The point estimate for the primary efficacy objective of prevention of the composite endpoint in the per protocol efficacy (PPE) population (which includes subjects that are both sero- and PCR-negative to the vaccine type being analyzed both before and during the 7 month period required for receipt of the full immunization series) was **88.7%** (95%CI: 78, 95). As noted above, the vast majority of cases (80 out of 86 cases in the control group) were either persistent infection or CIN1. Efficacy against HPV 6/11/16/18-associated CIN2+ in the PPE population was: Gardasil = 1, AAHS control = 6; **83.3%** (95%CI: -38, 100). These data demonstrate that the vaccine is effective in preventing vaccine type HPV infection and disease among individuals who were carefully selected based on a battery of proprietary assays to screen for evidence of current and/or past HPV exposure.

The clinical reviewer acknowledged the applicant's assertion that the PPE population is expected to have the least amount of confounding due to prevalent infection or disease, and therefore is the best test of efficacy for a prophylactic vaccine. However, the reviewer also noted that it will not be feasible in clinical practice to select a population comparable to PPE and to ensure that the vaccinated individuals remain sero- and PCR-negative to the vaccine types throughout the 7 month vaccination course.

Moreover, the applicant has not proposed nor studied a scenario wherein mid-adult women would be selected for receipt of the vaccine using commercially available assays, screening tests, or clinical triage algorithms. The potential for confounding bias thus works in the opposite direction to that asserted by the applicant. Removing subjects with prevalent infection or disease (such as in the PPE analyses) would tend to exaggerate the potential overall prophylactic efficacy of the vaccine in the general population. Therefore, the analyses conducted in the PPE population in this study are not expected to be predictive of vaccine effect in the general population.

Given these concerns about the PPE population, the analyses in the full analysis set (FAS) population were viewed as more clinically relevant. In the FAS analysis of the primary composite endpoint of HPV 6/11/16/18-related cases (driven, again, primarily by persistent infection), the results were Gardasil = 116, AAHS control = 214; **47.2%** (95%CI: 34, 58). Among the components of the composite, the incidence of genital warts was Gardasil = 7, AAHS control = 12; **41.8%** (95%CI: -60, 81); and CIN2+ incidence was Gardasil = 21, AAHS control = 27; **22.4%** (95%CI: -43, 58).

Finally, the reviewer acknowledged the importance of analyses of prevention of vaccine type (6/11/16/18)-associated infection and disease in terms of scientific proof of concept. However, HPV 16 and 18 are only two of the approximately 15 oncogenic HPV types that cause cervical dysplasia and cervical cancer. Therefore, the reviewer also analyzed

the potential impact of the vaccine taking into account infection and disease due to non-vaccine HPV types as well as vaccine types. In the FAS analysis of disease endpoints regardless of HPV type, the point estimates of efficacy were as follows:

CIN (any grade): Gardasil = 147, AAHS control = 155; **5.5%** (95%CI: -19, 25)
CIN2+ (any grade): Gardasil = 62, AAHS control = 51; **-21.5%** (95%CI: -80, 18)
genital warts: Gardasil = 12, AAHS control = 14; **14.5%** (95%CI: -99, 64)

Several other endpoints comprising outcomes due to any HPV type were evaluated in the FAS population, including prevention of abnormal Paps and prevention of definitive cervical or genital therapy; and the point estimates of efficacy were similarly low. The clinical reviewer concluded that the data suggest that the benefit of vaccination for older women in the prevention of vulvovaginal and cervical dysplastic disease due to HPV is likely to be insubstantial. Efficacy in the prevention of genital warts in this group also appears to be quite modest. The lack of significant efficacy in these particular analyses was an important factor in CBER's evaluation of this BLA supplement.

An important issue raised by the FAS analyses of disease due to any HPV type was the appearance of a higher number of cases of advanced dysplasia in the Gardasil group compared with the control group, referred to as reverse case splits. To evaluate this finding, the clinical reviewer performed a detailed analysis that is beyond the scope of this summary (see full clinical review for details). The primary finding was that randomization resulted in a larger burden of pre-existing infection and disease due to non-vaccine HPV types at baseline in the control group compared with the Gardasil group. The reviewer concluded that it is unlikely that the vaccine has a potentiating effect on disease due to non-vaccine HPV types. Even if such a phenomenon were real, the effect would be so diminutive compared with the effect of preventing HPV 16/18-related disease that it would be of negligible clinical significance. The reviewer commented that while the reverse case splits on cervical disease are unlikely to be clinically important, this observation supports the conclusion that increasing age and increasing prior exposure to HPV, which tend to track together, are both negatively correlated with potential benefit from vaccination.

Immunogenicity

The immunogenicity of Gardasil was measured using the applicant's proprietary competitive Luminex-based immunoassay (cLIA), which measures antibody titer against known neutralizing epitopes on the capsid surface. The assay has been validated as an indirect measure of total HPV neutralizing antibody titer; the applicant has used it throughout the clinical development program. Assay validation data was reviewed and accepted by CBER as part of the original Gardasil licensure. The primary immunogenicity endpoints assessed were as follows: (1) anti-HPV geometric mean titers (GMTs); and (2) seroconversion rate (SCR) at 4 weeks post-dose 3.

The seroconversion rate was uniformly high, with ≥96% of all subjects seroconverting against all 4 VLP types in all age strata. Immunogenicity data from mid-adult women subjects were compared with the data from younger women and adolescents by geometric mean titer (GMT). As expected, the immune response is less robust with increasing age.

The reviewer concluded that the clinical significance of the lower GMTs in older subjects remains unclear but is likely negligible.

Safety

The summary analysis of adverse events (AE) revealed a slightly higher overall rate of AEs among Gardasil recipients compared with placebo recipients. This was largely due to the higher rate of injection site AEs among Gardasil recipients compared with placebo recipients, as similar percentages in each group experienced a systemic AE or a serious adverse event (SAE).

Higher rates of injection site AE's among Gardasil recipients, driven largely by higher reporting rates for injection site pain, was also noted in the review of the young adult women data. The AEs resolved, and the rates of Grade 3 AEs were low. The data in mid-adult women are comparable, although the overall rates of injection site AEs are slightly lower in mid-adult women compared with younger women, indicating that mid-adult women may tolerate the vaccine better than younger women.

Analysis of the most common systemic AEs was unremarkable. The event rates of systemic AEs in the Gardasil group compared to the placebo group by system organ class (SOC) were similar.

Pregnancy outcomes were comparable to those observed in young adult women. Similar to the data in young adult women, there was a slight imbalance in cases of congenital anomalies: Gardasil = 5 (2.4% of live births); AAHS control = 4 (1.8% of live births). In the analysis of the young adult women data at the time of the submission of the original BLA, CBER reviewers, VRBPAC panelists, and a group of independent teratologists blinded to the intervention (Gardasil or placebo) received by study participants came to the same conclusions: that the widely divergent pathology among the cases, the consistency with commonly observed anomalies, the fact that no signal for teratogenicity was apparent in the preclinical reproductive toxicology studies, the fact that vaccine exposure was temporally remote from the gestational critical period in each case, and the fact that the rates were consistent with expected background rates did not suggest a safety signal with regard to congenital anomalies. In the context of the current submission, the clinical reviewer reached the same conclusion. With regard to the pregnancy outcomes data overall, there was no pattern of outcomes to suggest a safety signal.

Clinical Reviewer Overall Conclusions

Data submitted to the BLA supplement do not establish the efficacy of Gardasil in the prevention of advanced cervical dysplasia in women 27 to 45 years of age.

Data submitted to the BLA supplement do not establish a substantial likelihood of benefit in a general population of women aged 27 to 45 years on a number of other clinically important outcomes, such as prevention of genital warts, prevention of abnormal Paps, or prevention of definitive cervical or genital therapy.

It is possible that women 27 to 45 years of age who are relatively HPV naïve, as determined by medical/sexual history and by commercially available assays, may benefit from Gardasil, but benefit in that scenario was not definitively established by the data submitted to the BLA supplement.

The antibody response to Gardasil among women 27 to 45 years of age is less robust than among younger individuals, a phenomenon that is of uncertain, but likely negligible, clinical significance.

The safety profile of Gardasil in women 27 to 45 years of age is comparable to that in younger females. No safety signals were identified in the population studied for this BLA supplement.

6. Statistical

The statistical reviewer concluded that the data submitted to the BLA demonstrated efficacy of the vaccine in prevention of the composite endpoint (persistent infection, CIN, and EGL). However, the reviewer also concluded that none of the data submitted adequately addressed the issues raised in CBER's CR letters, namely that efficacy on the composite endpoint was driven primarily by persistent infection and that a higher number of any-HPV-type cases of CIN 2+ was observed in the Gardasil group compared to placebo.

7. Bioresearch Monitoring

----------Removed Per Privacy Act----------.

8. Labeling

The most substantial labeling issue concerned CBER's assessment that the data submitted to the sBLA does not support the expansion of the indications for Gardasil to women 27 to 45 years of age. CBER eventually reached consensus with the applicant that the "Limitations of Gardasil Use and Effectiveness" section should contain a statement about the *lack of demonstrated efficacy* on the advanced dysplasia endpoint in mid-adult women.

Recognizing the importance of informing health care providers and the public about the key findings from the clinical evaluation of Gardasil in mid-adult women, CBER concluded that immunogenicity, safety, and certain key efficacy data should be displayed in the package insert. Because the data suggested that there may be a weak beneficial effect among minimally HPV-exposed mid-adult women, especially if they are vaccinated prior to becoming sexually active with new partners, CBER agreed to display some specific endpoints from the Naïve to the Relevant HPV Type (HNRT) population analyses, e.g., prevention of persistent infection, prevention of CIN (any grade), and prevention of genital warts.

9. Postmarketing

The applicant recently completed a large postmarketing safety study, and the data are currently being reviewed by CBER. A number of other postmarketing commitments are in the process of being fulfilled. FDA maintains on its website a tool for tracking progress on postmarketing commitments and requirements: http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm

No safety signals were identified in the analysis of the data in mid-adult women. No further postmarketing action is required at this time.

10. Recommendation

The review committee recommended that the indications and usage of Gardasil not be extended to females 27 to 45 years of age.

Approval of the BLA supplement was recommended for revision of the package insert to display a limited set of data from the clinical study in women 27 to 45 years of age, as described in the labeling section (above).