Summary Basis for Regulatory Action

Date: April 24, 2015

From: Laura Montague, Chair of the Review Committee

BLA/ STN#: 125126/3096

Applicant Name: Merck Sharpe & Dohme Corp.

Date of Submission: June 26, 2014

PDUFA Goal Date: April 26, 2015

Proprietary Name/ Established Name: GARDASIL

Indication:
GARDASIL is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:

- Anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Wellington Sun, M.D., Director, DVRPA

☐ **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.**

Specific documentation used in developing the SBRA **Material Reviewed/Consulted**	**Reviewer Name – Document(s) Date**
Clinical Review	Sixun Yang, M.D. and Nancy Miller, M.D. 4/24/15
Statistical Reviews – Clinical and Assay	Zhong Gao, Ph.D. - 4/7/2015, 4/3/2015
CMC Review	Haruhiko Murata, M.D., Ph.D. – 4/16/2015
APLB Labeling Review	Dana Martin – 8/11/14

Cross referenced applications:

IND 9030, Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18; *S. cerevisiae*) L1 Capsid Virus-Like Particle Vaccine with Alum
BLA 125126/2870, Interim Report 2, V501-015-21 Study Report, 11/16/2012
BLA 125126/2954, Supplement to Interim Report 2, V501-015-21, 4/13/2013
BLA 125126/2269, Study Report through Month 72, V501-018-21, 12/2/2010

1. Introduction

GARDASIL®, Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant, is an aluminum adjuvanted non-infectious recombinant quadrivalent vaccine prepared from purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. It is available as a suspension in 0.5 mL single dose vials and prefilled syringes, for intramuscular administration in three 0.5 mL doses at months 0, 2, and 6.

On June 26, 2014, Merck Sharp and Dohme Corp. submitted 125126/3096, a Prior Approval Supplement (PAS) application to the Gardasil BLA. In this submission, Merck presents interim analysis data regarding Gardasil's persistence of effectiveness and persistence of immune responses from long term follow-up (LTFU) studies in support of updates to the Gardasil (Quadrivalent) Package Insert (PI). Merck proposes to describe the data in a new section, "Long Term Follow-up Studies," under the "Clinical Studies" section of the PI. No change to the current indication is proposed in this application. No updates to safety data are proposed.

2. Background

Gardasil was first licensed for use in the U.S. on June 8, 2006, and was originally indicated for use in females 9 to 26 years of age for prevention of cervical cancer, genital warts, and

precancerous or dysplastic lesions including cervical adenocarcinoma in situ (AIS), cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), and vaginal intraepithelial neoplasia (VaIN). With subsequent approvals of supplements in 2008, 2009, and 2010, the indication was expanded to include the prevention of vulvar, vaginal, and anal cancers and anal intraepithelial neoplasia (AIN), and the target population was expanded to include boys and men 9 to 26 years of age.

The duration of Gardasil's effectiveness and persistence of immune response had not been studied at the time of filing of the BLA. Therefore, when Gardasil was originally approved in 2006, Merck Sharp & Dohme committed to conduct studies to assess the persistence of effectiveness and immune response to the vaccine. Consistent with post marketing commitments specified in the June 8, 2006 Gardasil approval, several Phase 3 studies were extended in order to assess the persistence of effectiveness and immunogenicity of Gardasil.

In this submission, Merck Sharp & Dohme presents interim data from two on-going extension studies, V501-015-21 and V501-018-11, and proposes to include the data in the PI. Both studies are extensions of Phase 3 studies and follow individuals who were vaccinated in the base studies to monitor for disease endpoints and immune responses. In base study V501-015, young women 16 to 23 years of age were vaccinated with Gardasil. Interim data from the extension study, V501-015-21 are presented in this submission. When complete, data from this study will provide 14 years of follow-up from the time of the last patient enrollment in the base study. In base study V501-018, male and female adolescents 9-18 years of age were vaccinated with Gardasil. The Month 96 results from extension study V501-018-11 are presented in this submission. At the completion of the extension study, it will provide data through Month 126. Additionally, the applicant presents interim results from two additional ongoing extension studies, V501-020-21 and V501-019-21. These interim data are not intended to inform changes to the package insert. Rather, they were submitted to support overall conclusions of continued effectiveness and sustained immunogenicity regardless of subject population.

The interim reports include data with clinical endpoints and type-specific anti-HPV antibody titers as measured by competitive Luminex immunoassay (cLIA). In addition, this submission includes data generated from a new assay, (b) (4) (b) (4) The new assay was used to measure (b) (4) collected 8 and 9 years post-dose 1, for comparison to levels measured by the cLIA assay. Data generated from the (b) (4) are not presented in the PI.

3. Chemistry Manufacturing and Controls (CMC)

No manufacturing changes were proposed in this supplement, and no manufacturing information was submitted.

4. Nonclinical Pharmacology/Toxicology

No toxicology studies were performed in support of this supplement.

5. Clinical Pharmacology

No clinical pharmacology information was provided in the supplement.

6. Clinical/ Statistical

a) Clinical Program

This supplemental Biological Licensing Application (BLA) provides interim data and analyses from on-going extension studies in support of modifications to the Gardasil PI. The extension studies were designed to evaluate persistence of effectiveness and immunogenicity and safety of Gardasil. Data from two long-term effectiveness studies, V501-018-11 and V501-015-21, showed that Gardasil continued to be effective in prevention of vaccine HPV-related disease over time, that cLIA type-specific seropositivity rates decreased only modestly over time, and that no new safety concerns were identified.

Study V501-015-21 is a follow-up extension of the V501-015 base study. It uses national healthcare registries in Denmark, Iceland, Norway, and Sweden to monitor endpoint cases of HPV 6-, 11-, 16-, or 18-related cervical intraepithelial neoplasia (CIN) (any grade), adenocarcinoma *in situ* (AIS), cervical cancer, vulvar cancer, or vaginal cancer, and to evaluate the long-term anti-HPV 6, 11,16, and 18 immune responses generated by Gardasil in girls and women who were 16 through 23 years of age when enrolled in the base study.

Study V501-018-11 is a follow-up extension of the V501-018 base study, to evaluate anti-HPV 6, 11, 16, and 18 antibody levels, effectiveness, and safety of Gardasil up to 10 years following vaccination in male and female subjects who were 9 to 15 years old when enrolled in the base study.

Persistence of Effectiveness: In an interim analysis of study V501-015-21, the median follow-up from initial vaccination was 6.7 years with a range of 2.8 to 8.4 years. No cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, or vaginal cancer were observed in the Per Protocol Efficacy (PPE) population of 1,902 subjects (representing a total of 5,765 person-years at risk). The PPE population in this study comprised subjects who completed the Gardasil vaccination series within one year, were naïve to the relevant HPV type through 1 month post-dose 3, had no protocol violations, and had follow-up data available.

A total of 1,116 subjects who received 3 doses of Gardasil in the V501-018 base study were followed in the extension study V501-018-11. The median follow-up time from the first dose of vaccine was 7.2 years with a range of 0.5 to 8.5 years. Effectiveness analyses at Month 96 showed that in the PPE population no cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade) or external genital lesions (EGL) were observed. The PPE population in this study comprised subjects who completed the Gardasil vaccination series within one year, were seronegative to the relevant HPV type at initiation of the vaccination series, and had not initiated sexual activity prior to receiving the third dose of Gardasil, Four cases of vaccine HPV type-related persistent infections with duration of at least 6 months were reported through Month 96; two cases of HPV 16-related persistent infection in females, one case each of HPV 6- and 16-related persistent infection in males. No cases of persistent infection of at least 12-months were reported.

Persistence of the Immune Response: Immunogenicity analyses were conducted using the Competitive Luminex Immunoassay (cLIA) that has been used for immunogenicity analyses throughout the Gardasil development program. Geometric mean titers (GMTs) as measured by cLIA demonstrate evidence of persistence of immune responses at 8 years post-dose 1 in study V501-018-11 and at 9 years post-dose 1 in study V501-015-21, with an overall trend of

decrease over time. The proportion of subjects remaining seropositive at 8 or 9 years post-dose 1, as measured by cLIA, ranged from 88.4% to 94.4% for anti-HPV 6, from 89.1% to 95.5% for anti-HPV 11, from 96.8% to 99.1% for anti-HPV 16, and from 60.0% to 64.1% for anti-HPV 18.

Supportive Studies not included in modified label:
Merck submitted interim reports for two additional long-term follow-up studies; one in mid-adult women 27 through 45 years of age at the time of vaccination (V501-019-21), and the second in young men 16 through 26 years of age at the time of vaccination (V501-020-21). Interim results from these ongoing studies were submitted to support the overall conclusions from V501-015-21 and V501-018-11, but were not included in the modified PI. Similar to the interim long-term results in young women (V501-015-021) and adolescents (V501-018-11), no HPV 16- or HPV 18-related pre-cancerous lesions were observed through six years of follow-up in mid-adult women and young men. Also similar to the studies in young women and adolescents, seropositivity rates by cLIA in mid-adult women and young men modestly decreased over time, with more substantial decreases for HPV-18.

b) Clinical Assays

In this submission, Merck introduced a new immunogenicity assay, the (b) (4). These data were submitted as supportive evidence to explain the greater decrease over time in seropositivity rate for HPV type 18 compared to the other types when measured by the historically-used cLIA assay. Merck suggested that the neutralizing epitope for HPV type 18 targeted by cLIA may not be immunodominant, and thus, antibodies against this epitope as measured by cLIA may diminish over time. However, Merck provided (b) (4) data only for sera collected at Months 96 and 108, but did not provide (b) (4) data from prior time points. Although information regarding the (b) (4) and data derived from its use were presented in the submission and proposed for inclusion in the PI, ultimately the (b) (4) data were not included in the modified PI because (b) (4) data from prior time points were not available for comparison.

c) Pediatrics

This supplement reports interim results of postmarketing commitment studies and does not change the licensed indication, dose, regimen, formulation, or route of administration. Therefore, an assessment as per the requirements of PREA did not apply to this supplement.

d) Bioresearch Monitoring Review

No bioresearch monitoring inspections were deemed necessary by the review committee.

7. Safety

In the data presented in this submission, no signals of new medical conditions, new SAEs assessed as vaccine-related, or other new safety signals were identified. No new safety information was proposed to be included in the modified USPI.

8. Advisory Committee Meeting

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting because review of this submission did not identify concerns which would have benefitted from an advisory committee discussion.

9. Other Relevant Regulatory Issues

There are no additional relevant issues.

10. Labeling

The applicant submitted a modified PI, proposing the addition of a new section, "Long Term Follow-up Studies," under the "Clinical Studies" section of the package insert. No updates to safety data were proposed. No patient package insert (PPI), carton, or container labels were submitted. Review committee members participated in internal labeling discussions and concurred that the applicant's revised proposed PI submitted on April 6, 2015 is acceptable.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

It is the consensus of the review committee that the supplement be approved and that long-term interim effectiveness and immunogenicity data be included in the package insert.

b) Risk/ Benefit Assessment

The risk-benefit summary remains positive for Gardasil; the benefit of the vaccine outweighs the risks of receipt of the vaccine. There is evidence of continued effectiveness and persistence of immune responses, and no new safety signal is noted in the long term extension studies.

c) Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are recommended.

d) Recommendation for Postmarketing Activities

No additional post-marketing actions are recommended. The long-term follow-up studies reviewed in this BLA supplement are ongoing, and additional data will be submitted at a later time.