Summary Basis of Regulatory Action

Date: December 14, 2015
From: Laura Montague, Chair of the Review Committee
BLA/ STN#: 125508/15

Applicant Name: Merck Sharpe & Dohme Corp.

Date of Submission: February 13, 2015
PDUFA Goal Date: December 14, 2015

Proprietary Name: GARDASIL 9
Established Name: Human Papillomavirus 9-valent Vaccine, Recombinant

Indication:
In this submission, the Applicant proposes to extend the current indication to include males 16 through 26 years of age for the prevention of the following diseases:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
- 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, 18, 31, 33, 45, 52, and 58:

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

Recommended Action: Approval

Signatory Authorities Action: Approval

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

☐ **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	**Reviewer Name**
Clinical Review	Sixun Yang, M.D., Ph.D.
Statistical Review	Lihan Yan, Ph.D.
Bioresearch Monitoring Review	Erin McDowell
Labeling – APLB review	Dana Martin

Cross referenced applications:

IND 9030, Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18; *S. cerevisiae*) L1 Capsid Virus-Like Particle Vaccine with Alum

IND 13447, Human Papillomavirus Recombinant L1 Nine-Valent (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58; *Saccharomyces cerevisiae*) Virus-Like Particle Vaccine with Alum Adjuvant

BLA 125126, Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant, GARDASIL®

1. Introduction

GARDASIL 9 is a non-infectious recombinant 9-valent Human Papillomavirus (HPV) vaccine prepared from purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The VLPs are adsorbed on amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant. GARDASIL 9 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.

GARDASIL 9 was first licensed for use in the U.S. on December 10, 2014 for the prevention of the following diseases:
For girls and women 9 through 26 years of age:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
- 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, 18, 31, 33, 45, 52, and 58:

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

For boys 9 through 15 years of age:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.

AIN grades 1, 2 and 3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

In this supplemental application, submitted February 13, 2015, the Applicant proposed to expand the GARDASIL 9 indication to include young men 16 through 26 years of age in the target population. Upon approval, the population approved for the use of the vaccine would include individuals 9 through 26 years of age. To support the addition of young men 16 through 26 years of age to the population approved for use of Gardasil 9, the Applicant has submitted the final clinical study report for Study V503-003, in which the safety and immunogenicity of Gardasil 9 in young men16 though 26 years of age was compared to that in females 16 through 26 years of age. To support the transition of long-term Gardasil effectiveness information from the Gardasil package insert (PI) to the Gardasil 9 PI, interim study reports for V501-018-11, and V501-020-21 were included in submission. Those study reports were reviewed previously, and the results are reflected in the current version of the Gardasil PI. Therefore, the study reports were not reviewed in the context of this submission. No change to the formulation or immunization regimen was proposed in this application.

2. Background

HPV infection causes benign and malignant dysplastic anogenital disease in men and women. Nearly 100% of cervical cancers and 90% of anal cancers are caused by oncogenic HPV types. In males, the HPV-related disease burden includes anogenital warts, anal intraepithelial neoplasia (AIN) and anal cancer.

Gardasil 9 is the second HPV vaccine manufactured by Merck Sharp & Dohme approved for use in the U.S. Prior to the licensure of Gardasil 9, Merck's 4-valent HPV vaccine, Gardasil, was licensed in 2006. Gardasil protects against disease caused by HPV Types 6, 11, 16, and 18. GARDASIL 9 includes the original four HPV types in Gardasil, plus an additional five types, HPV 31, 33, 45, 52, and 58.

Gardasil 9 was first licensed for use on December 10, 2014, with an indication to prevent disease related the HPV types in the vaccine in girls and women 9 through 26 years of age, and boys 9 through 15 years of age. For girls and women 16 through 26 years of age, efficacy of Gardasil 9 against genital lesions due to HPV types 31, 33, 45, 52, and 58 was demonstrated directly in a Gardasil-controlled clinical endpoint efficacy trial, while effectiveness of Gardasil 9 against anal pre-cancerous lesions and cancers due to HPV types 31, 33, 45, 52, and 58 was inferred from antibody responses elicited by Gardasil 9 against those HPV types, together with the previously demonstrated efficacy of Gardasil against anal pre-cancerous lesions and cancers due to HPV types 16 and 18. The effectiveness of Gardasil 9 against anogenital lesions due to HPV types 6, 11, 16, and 18 in girls and women 16 through 26 years of age was inferred through non-inferiority immunobridging from Gardasil. For girls and boys 9 through 15 years of age, effectiveness of Gardasil 9 against anogenital lesions due to all HPV types covered by the vaccine was inferred through non-inferiority immunobridging from girls and women 16 through 26 years of age.

In this supplement, the Applicant presents data from Study V503-003, in which approximately 1,400 boys and men 16 through 26 years of age, and 1,100 girls and women 16 to 26 years of age were enrolled. The effectiveness of Gardasil 9 in boys and men 16 through 26 years of age was inferred by immunobridging from girls and women 16 through 26 years of age via non-inferior immunogenicity comparison. This strategy was discussed and agreed upon in a meeting held between CBER and the Applicant in July 2011.

3. Chemistry Manufacturing and Controls (CMC)

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

4. Nonclinical Pharmacology/Toxicology

No toxicology studies were needed or performed in support of this supplement.

5. Clinical Pharmacology

No clinical pharmacology information was needed or provided in this supplement.

6. Clinical/ Statistical

a) Clinical Program

In study V503-003, an immunological bridging strategy is used to infer effectiveness in boys and men 16 through 26 years of age by non-inferiority immunogenicity comparison with girls and women 16 through 26 years of age, the population in which efficacy and effectiveness have previously been established.

Study V503-003

To support extending the current Gardasil 9 indication to include males 16 through 26 years of age, Merck submitted the final clinical study report of Study V503-003, a phase 3, open-label international, multicenter clinical trial in which approximately 1100 healthy subjects 16 through 26 years of age who self-identified as heterosexual men (HM) and 1100 healthy girls and women 16 through 26 years of age were enrolled. In addition, approximately 300 subjects 16 through 26 years of age who self-identified as men having sex with men (MSM) were enrolled and evaluated separately. Gardasil 9 was administered to study subjects as a 0.5-mL intramuscular injection at Day 1, Month 2, and Month 6. Serum samples were collected at Day 1 (pre-vaccination) and Month 7 (week 4 post-dose 3). Seventy-six centers participated in the study, including 24 in the U.S. Other centers were located in Canada, Colombia, Denmark, Germany, Israel, Malaysia, Mexico, Norway, Peru, Philippines, Poland, South Africa, Spain, Sweden, Thailand, and Turkey.

The primary objectives of the study were (1) to evaluate the tolerability of Gardasil 9 in boys and men 16 through 26 years of age in comparison to girls and women 16 through 26 years of age, and (2) to demonstrate that Gardasil 9 induces non-inferior Geometric Mean Titers (GMTs) for antibodies to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 in HM 16 through 26 years of age, compared to girls and women 16 through 26 years of age. Secondary objectives were (1) to demonstrate that Gardasil 9 induces non-inferior antibody responses in HM 16 through 26 years of age with respect to seroconversion percentages to the HPV types covered by the vaccine compared to the antibody responses in girls and women 16 through 26 years of age, and (2) to evaluate the antibody response to the Gardasil 9 HPV types at Month 7 in MSM subjects.

Safety endpoints included injection site and systemic reactions, new onset of medical conditions including potential autoimmune disorders, and serious adverse events (SAEs). Safety results for V503-003 will be discussed in section 7 of this document.

Immunogenicity Assessments in Young Men and Young Women

The primary immunogenicity endpoint for evaluating antibody response to Gardasil 9 were GMTs for antibodies to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Month 7. The statistical criterion for non-inferiority required that the lower bound of the two-sided 95% confidence interval (CI) of GMT ratio (GMT of HM 16- through 26 years of age/ GMT of girls and

women 16 through 26 years of age) be greater than 0.67 for each HPV type. The results of study V503-003 showed that in the per-protocol immunogenicity (PPI) population, anti-HPV GMT ratios of HM to girls and women for the 9 HPV types in the vaccine ranged from 1.09 to 1.27. The lower bound of the 95% CI for all 9 HPV types was above 0.67 and thus the study met the success criteria for the primary endpoint. These results support the bridging of effectiveness that was established in 16 to 26 year old girls and women in the original BLA submission to HM 16 through 26 years of age.

The secondary immunogenicity endpoints for evaluating antibody response to Gardasil 9 were the percentages of subjects who seroconverted for each HPV type (6, 11, 16, 18, 31, 33, 45, 52, and 58) by Month 7. Seroconversion was defined as a change in serostatus from seronegative at baseline to seropositive by Month 7. A subject with a GMT at or above the serostatus cutoff for a given HPV type was considered seropositive for that type. The statistical criterion for non-inferiority required that the lower bound of the two-sided 95% CI for the difference (HM minus girls and women) in seroconversion percentages be greater than -5.0 percentage points for each HPV type. The results of Study V503-003 show that seroconversion rates in both groups to all 9 HPV types were above 99%, and the pre-specified success criteria of non-inferiority were met; the estimated point differences between the seroconversion rates for the two groups for each of the 9 HPV types ranged from 0.1 to 0.2 with the lower bound of the 95% CI ranging from -0.2 to -0.7.

Immunological Assessment in MSM

Results of a clinical study of the 4-valent HPV vaccine, Gardasil, showed that antibody responses are reduced in MSM subjects compared to HM subjects. In V503-003, antibody responses to Gardasil 9 in MSM were evaluated in a separate analysis. Results showed that the GMT ratios of MSM/girls and women for each HPV type ranged from 0.70 to 0.89, and the GMT ratios of MSM/HM for each HPV type ranged from 0.59 to 0.75. However, over 99% of subjects in all 3 groups (HM, MSM, and girls and women) seroconverted to all 9 vaccine HPV types. These results are consistent with those seen in prior Gardasil studies comparing immunogenicity in the HM and MSM populations. Given that the efficacy of Gardasil has been demonstrated directly in MSM in preventing persistent infection, condyloma, anal pre-cancer and anal cancer related to the vaccine HPV types covered by that vaccine, and that the immunogenicity profile of Gardasil 9 in MSM vs. HM is similar to that of the Gardasil in the same populations, the effectiveness of Gardasil 9 in MSM is inferred.

b) Pediatrics

Gardasil 9 has been adequately studied in the pediatric population 9 through 16 years of age. A partial waiver from assessments in children 0 through 8 years of age was granted in with the original BLA approval.

There was no change in active ingredient, indication, dosage form, dosing regimen, or route of administration in this study. Therefore, PREA was not triggered by this submission.

c) Bioresearch Monitoring Review

CBER Bioresearch Monitoring (BiMo) issued five inspections in support of this Biologics Licensing Application supplement (sBLA). The clinical sites inspected were located in Spain,

Malaysia, Philippines, and United States (Florida and California). The BiMo inspections did not reveal significant problems that impact the data submitted in this marketing application.

7. Safety

A primary objective of Study V503-003 was to evaluate the tolerability of Gardasil 9 in all study subjects. To assess the safety of the vaccine, subjects were monitored for serious adverse events (SAEs) and new medical conditions, regardless of causality, from Day 1 through Month 12 (6 months after the third vaccination). Each subject was to record his/her oral temperature from Day 1 to Day 5 following each injection on a Vaccine Report Card (VRC). Subjects were also to use the VRC to record any injection-site and systemic adverse events from Day 1 through Day 15 following each injection. Injection-site pain, erythema, and swelling were specifically solicited on the VRC. Additionally, females were monitored for pregnancy outcomes; any fetal loss was to be reported as an SAE for all pregnancies with a last menstrual period (LMP) between Day 1 and Month 12.

Generally, in Study V503-003, 16 through 26 year-old boys and men reported fewer adverse events than 16 through 26 year-old girls and women. Also, the proportion of subjects reporting at least one systemic adverse event within 15 days of any injection was numerically lower in boys and men (75.4%) compared with girls and women (88.7%).

Injection-site Adverse Reactions

The most common injection-site adverse reactions reported were the solicited injection-site reactions of pain (63.4% in boys and men vs. 82.5% in girls and women), erythema (20.7% in boys and men vs. 32.2% in girls and women), and swelling (20.2% in boys and men vs. 37.5% in girls and women). The proportion of subjects who reported at least one injection-site adverse reaction within 15 days of any injection was numerically lower in boys and men (67.6%) compared with girls and women (84.1%). The rates of injection-site pain, erythema, and swelling reported in girls and women in V503-003 were similar to those reported in the same age range population of girls and women in the original Gardasil 9 BLA.

Systemic Adverse Reactions

The most common systemic adverse reactions reported in Study V503-003 that were considered to be vaccine-related by the investigator were headache and pyrexia, which occurred at lower frequencies in boys and men than in girls and women. Headache was reported at a rate of 14.3% in boys and men, and at a rate of 22.9% in girls and women. The frequency of pyrexia in boys and men was 3.6%, and in girls and women was 4.7%. Girls and women also experienced nausea at a rate of 4.7%, and the rate of nausea in boys and men was 1.5%. The rate of any grade fever in boys and men was 4.4% compared with a rate of 5.9% in girls and women. The overall profile of vaccine-related systemic clinical adverse reactions was generally similar across the two groups.

Serious Adverse Events (SAEs)

No subject died during the course of Study V503-003.

Thirty-eight subjects (23 boys and men and 15 girls and women) experienced serious adverse experiences during the entire study period. This included 8 subjects who experienced SAEs within 30 days of a Gardasil 9 injection (5 subjects in the boys and men cohort and 3 subjects in the girls and women cohort). The most common SAEs among the 16 to 26 year-old boys and men were appendicitis and concussion. The most common SAEs among the 16 to 26 year old girls and women were appendicitis and constipation. None of the serious adverse events were considered related to the study vaccine according to the investigators. Following review of the available information, CBER concurred that the SAEs reported in this study were unlikely related to the vaccine.

Fetal Loss

Pregnancy outcomes were followed for all pregnancies reported or detected from Day 1 through Month 12 of the study. Overall, 35 subjects reported 39 pregnancies. Outcomes were available for 33 of the 39 pregnancies. There were no reports of late fetal death, congenital anomaly, or other abnormalities. No serious adverse events were reported for any of the infants born to study subjects.

Of the 33 pregnancies with known outcome, 22 pregnancies led to a live birth, and 11 pregnancies led to a fetal loss. Of the 11 fetal losses, four were induced abortions, five were spontaneous abortions (including one incomplete abortion) and two were ectopic pregnancies. None of the five subjects who experienced spontaneous abortions received a vaccination within 30 days of the estimated date of conception. None of these events were considered related to the study vaccine by the individual reporting investigator. The rate of spontaneous abortion in this study was 15.2% (5 out of 33 pregnancies with known outcome), which was numerically higher than that the rates observed among Gardasil 9 recipients (10.4%) and Gardasil recipients (12.9%) in the studies submitted with the original BLA submission. However, the clinical significance of this difference is unknown because of the limited number of cases that occurred in this study. Following review of the available information, CBER concurs with the reporting investigators that the fetal losses reported in this study were unlikely related to the vaccine.

Discontinuation due to Adverse Events

Five subjects did not complete the 3-dose regimen of Gardasil 9 due to a non-serious clinical adverse reaction. The events were injection-site pain, erythma and swelling, urticaria, depressive symptom, and injection-site nodule and pain. All the adverse reactions in the five subjects were considered by the individual investigators to be vaccine-related. The CBER clinical reviewer reviewed the narrative summaries for all five subjects and concurred with the investigators' assessments.

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 or issues which would have benefitted from an advisory committee discussion.

9. Other Relevant Regulatory Issues

N/A

10. Labeling

The package insert (PI) and patient information (PPI) with all changes necessitated by inclusion of the data in support of addition of boys and men 16 through 26 years old to the Gardasil 9 indication were reviewed by relevant members of the review committee, including clinical, statistical, and APLB reviewers. The revised Gardasil 9 PI approved with this supplement incorporates information from V503-003 into the Clinical Trials Experience section of the Adverse Reactions section and into the Clinical Studies section. The Clinical Studies section was also revised to include information previously approved for inclusion in the Gardasil PI regarding longer-term effectiveness of Gardasil. The PPI was revised to reflect the inclusion of 16 through 26 year old boys and men in the target population. Minor changes to improve clarity and consistency were made throughout the PI and PPI. The committee concurs that the PI and PPI submitted on 12/09/2015 are acceptable.

No changes to the carton/container labels were proposed in this supplement.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

It is the consensus of the review committee to approve this supplemental application to add boys and men 16 through 26 years old to the Gardasil 9 indication.

b) Risk/ Benefit Assessment

The benefit/risk balance for Gardasil 9 is favorable for use in boys and men 16 through 26 years of age. On the basis of the data from this submission, Gardasil 9 is effective in preventing HPV 6 and 11 related genital warts and HPV 16, 18, 31, 33, 45, 52, and 58-related anal cancers, and the high-grade pre-cancers that immediately precede them. The proposed indication for Gardasil 9 is supported by the data presented in this application. The most common adverse reactions observed with Gardasil 9 in the proposed population are injection site reactions (pain, swelling and erythema), headache, pyrexia, and nausea. These adverse reactions are typically mild to moderate, and resolve within several days. The review committee concludes that the benefit offered by Gardasil 9 in boys and men 16 through 26 years of age outweighs its risks.

c) Recommendation for Postmarketing Risk Management Activities

No safety issues have been identified that would have warranted a Risk Evaluation and Mitigation Strategy (REMS) or a new Postmarketing Requirement (PMR).

d) Recommendation for Postmarketing Activities

Post-marketing activities for Gardasil 9 were established at the time of the approval of the original BLA in December 2014. No new postmarketing assessment is recommended at this time.