Summary Basis for Regulatory Action

Date: October 5, 2018

From: Laura Montague, Chair of the Review Committee

STN#: 125508/493

Applicant Name: Merck Sharpe & Dohme Corp.

Date of Submission: April 6, 2018

Goal Date: October 6, 2018

Proprietary Name: GARDASIL 9

Established Name: Human Papillomavirus 9-valent Vaccine, Recombinant

Indications and Usage:
This supplement includes safety, effectiveness and immunogenicity data to extend the current indications and usage of GARDASIL 9 to include men and women 27 through 45 years of age, as follows:

GARDASIL 9 is indicated in girls and women 9 through 45 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (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 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 9 is indicated in boys and men 9 through 45 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:
The Review Committee recommends approval of this supplement to extend the indications and usage for GARDASIL 9 to include individuals 27 through 45 years of age.

Review Offices Signatory Authority: Doran Fink, MD, PhD, Deputy Director (Clinical), DVRPA <ESIG>

X 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.

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name**
Assay Review (product)	Haruhiko Murata, MD, PhD
Bioresearch Monitoring Review	Christine Drabick
Clinical Review	Joohee Lee, MD
Facilities review (for categorical exclusion)	Ekaterina Allen, PhD
Labeling Review – OCBQ/APLB	Oluchi Elekwachi
Pharmacovigilance Review	Adamma Mba-Jonas, MD, MPH
Statistical Reviews • Clinical data • Assay Validation	 Sang Ahnn, PhD Ye Yang, PhD

Cross referenced application:
BLA 125126, Human Papillomavirus Quadrivalent (Types 6, 11, 16 and 18) Vaccine, Recombinant, GARDASIL®.

1. Introduction

Merck Sharp & Dohme (Merck) manufactures two licensed Human Papillomavirus Vaccines; quadrivalent HPV vaccine (GARDASIL, HPV types 6/11/16/18; STN 125126), and 9-Valent HPV Vaccine (GARDASIL 9; HPV types 6/11/16/18/31/33/45/52/58; STN 125508). GARDASIL was licensed in 2006, but is no longer distributed in the US.

GARDASIL 9, licensed in 2014, is a non-infectious recombinant nine-valent vaccine prepared from purified virus-like particles (VLPs) of the major capsid (L1) protein of Human Papillomavirus (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.

In individuals 9 through 14 years of age, GARDASIL 9 can alternatively be administered as a 2-dose regimen.

In this supplemental application, Merck proposed to extend the current indication and usage of GARDASIL 9 to include individuals 27 through 45 years of age. In support of the application, Merck referenced results of a 4-year-long "base study" (V501-019) in which 24- through 45-year-old women were randomized to receive GARDASIL or placebo (AAHS). Results from study V501-019 were previously reviewed under STN 125126/773 (see Background for more details). In this application, Merck submitted the results of a long-term follow-up (LTFU) extension of study V501-019. Merck also referenced results of study V501-108, in which men 27 through 45 years of age were vaccinated with GARDASIL, and they presented a cross-study analysis of serum type-specific antibody levels (see CMC section) comparing Month 7 geometric mean titers (GMTs) to HPV types 6, 11, 16, and 18 in 27- through 45-year-old men (V501-108) to those from boys and young men 16 through 26 years of age vaccinated with GARDASIL (V501-020). No changes to the manufacturing and formulation of GARDASIL 9 were proposed in this application.

2. Background

Human papillomavirus (HPV) infection is a common sexually transmitted infection that causes benign and malignant dysplastic anogenital disease in men and women. High-risk HPV types are oncogenic, and certain low-risk HPV types, particularly HPV 6 and 11, can cause anogenital warts. High-risk HPV types 16, 18, 31, 33, 45, 52, and 58 are the most commonly detected in cervical cancers globally. About 70% of cervical cancers are attributed to HPV 16 and 18, which are covered by both GARDASIL and GARDASIL 9. About 20% of cases of cervical cancers are attributed to HPV types 31, 33, 45, 52, and 58, which are covered by GARDASIL 9. In the United States, HPV 16 and 18 are detected in about 50% of high-grade cervical lesions, including cervical intraepithelial neoplasia (CIN) grades 2 and 3 and adenocarcinoma in situ (AIS), and the other 5 high-risk types covered by GARDASIL 9 are detected in about 25% of high-grade cervical lesions.

HPV infections in mid-adult individuals (defined for the purpose of this document as 27 through 45 years of age) can appear to be the result of new exposure when they actually represent reactivation of latent HPV infection that was previously undetectable. In the past, the magnitude of this phenomenon was poorly characterized. Newer data indicate that a large portion of HPV infections in mid-adult women are due to newly acquired infections, rather than reactivation. For example, a recent study of a group of women online daters 25 to 65 years of age reported a 12-month incidence of high-risk HPV in vaginal swabs of 25.4% (95% CI: 21.3, 30.1), of which 64% were likely new acquisitions, and about one-third were likely re-detections of prior infection (Winer, J. Infect. Dis., 2016; 214(5)). Men in mid-adulthood also have a substantial burden of new HPV infections. The 2013-2014 National Health and Nutrition Examination Survey of 1757 men aged 18 to 59 years in the US estimated an overall prevalence of genital HPV infection of 45.2% (95% CI, 41.3% - 49.3%). HPV prevalence in these men followed a bimodal pattern, first peaking at 28 to 32 years of age, followed by a greater second peak at 58 to 59 years of age (Han *et al.*, JAMA Oncol. 2017; 3(6)). These epidemiological data

indicate the potential for clinically meaningful benefit of prophylactic vaccination against HPV in mid-adult women and men.

Merck's first licensed HPV vaccine, GARDASIL, was approved in June 2006 for use in girls and women 9 through 26 years of age, for prevention of HPV-related diseases caused by the four HPV types covered by the vaccine. Clinical efficacy against cervical cancer, genital warts, CIN 2/3, VIN 2/3, VaIN 2/3 and CIN 1 was demonstrated in girls and women 16 through 26 years of age, and effectiveness was inferred through immunobridging to girls 9 through 15 years of age by demonstrating non-inferior antibody responses to vaccine-type HPV in the younger group compared to the older group in which efficacy had been established. Prevention of vaginal and vulvar cancers in women was added to the indication in 2008 (STN 125126/419), use in males and prevention of genital warts were added to the indication in 2009 (STN 125126/1297), and prevention of anal cancer and AIN in men and women was added to the indications and usage in 2010 (STN 125126/1895). For the first two indications, clinical efficacy was demonstrated in 16 through 26-year-old women and men and effectiveness inferred in 9 through 15-year-old girls and boys through immunobridging. For the indications for anal cancer and AIN, clinical efficacy was demonstrated in boys and men 16 through 26 years of age, effectiveness was inferred through immunobridging in boys 9 through 15 years of age, and effectiveness was extrapolated to girls and women 9 through 26 years of age based on epidemiological, histological, and pathophysiological data regarding HPV disease in male and females.

A similar approach of establishing efficacy and immunobridging was used in the GARDASIL 9 program. In 2014, GARDASIL 9 was licensed with indications to prevent diseases related to the HPV types covered by the vaccine in girls and women 9 through 26 years of age, and boys 9 through 15 years of age. In women 16 through 26 years of age, efficacy of GARDASIL 9 for the 5 additional oncogenic HPV types in the vaccine was demonstrated by comparing to Gardasil in a blinded, randomized trial in which prevention of type-specific CIN2+ disease was the primary endpoint. For the original 4 HPV types common to both vaccines, effectiveness was inferred through immunobridging, by demonstration that the geometric mean titers (GMTs) for antibody responses in GARDASIL 9 recipients were non-inferior to GARDASIL recipients. The effectiveness of GARDASIL 9 in girls and boys 9 through 15 years of age was also inferred through immunobridging, by demonstration that all 9 HPV type-specific GMTs were non-inferior to those observed in women 16 through 26 years of age.

In 2015, the GARDASIL 9 indications applicable to males were extended to include men 16 through 26 years of age (STN 125508/15). Effectiveness in 16 through 26-year-old men was inferred based on non-inferior HPV type-specific GMTs compared to girls and women of the same age. A similar approach was also used to infer effectiveness of the 2-dose regimen in girls and boys 9 through 14 years of age (STN 125508/153).

To support extending the upper age limit for the GARDASIL 9 indications to 45 years of age, this application includes data from one study conducted in two phases: a four-year-long base study (V501-019) in which women 24 through 45 years of age were vaccinated with GARDASIL or placebo, and a long-term follow-up (LTFU) extension study (V501-

019-21) in which a subset of women enrolled in the base study were followed up to an additional six years.

Results of the base study were previously submitted to CBER in 2008 in STN 125126/773. After CBER's review, information from study V501-019 was included in the GARDASIL package insert (PI) to better inform health care providers and the public regarding use of GARDASIL in minimally HPV-exposed women 27 through 45 years of age. However, under 125126/773, the GARDASIL indications were not extended to include use in women up to 45 years of age due to uncertainty related to the potentially concerning observation of more cases of CIN2+ due to non-vaccine types in the vaccine group compared with the placebo group (See Section 6a. Clinical Program, below).

In this application, Merck submitted the results of the LTFU study and proposed that the LTFU data, combined with current information on HPV epidemiology and information from previous studies of GARDASIL and GARDASIL 9, support extending the current GARDASIL 9 indication to include individuals 27 through 45 years of age. Merck also proposed to infer effectiveness in men 27 through 45 years of age from efficacy data for GARDASIL in women, and they provided support by referencing study V501-108, in which immunogenicity and safety of GARDASIL was assessed in men 27 through 45 years of age. In a cross-study analysis, immunogenicity results from study V501-108 were compared to those from an earlier study (V501-020) of 16- through 26-year-old men in whom clinical efficacy of GARDASIL to prevent vaccine-type HPV-related anogenital disease had been demonstrated.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

No manufacturing changes have been proposed in this supplement; therefore, no manufacturing information was needed or was submitted for review.

In the studies used to support this application, type-specific immunoassays (i.e., competitive Luminex immunoassays, cLIA) were used to assess serum antibody responses to each vaccine HPV type. These assays measure antibodies against neutralizing epitopes for each HPV type. Immunogenicity was analyzed using Geometric Mean Titers (GMT). Multiplex HPV PCR assays were used to detect DNA for a given HPV type. PCR positive is defined as DNA detected for a given HPV type, and PCR negative is defined as DNA not detected for a given HPV type.

The cLIA and PCR assays used to support this application were reviewed by CMC and statistical reviewers. Both reviewers concluded that the validation/qualification reports of the assays relevant to this submission had been previously reviewed in the context of other submissions, and no new concerns related to the assays were identified. The CMC reviewer concluded that the assays used are suitable for the assessment of clinical study endpoints.

a) Product Quality

N/A

b) CBER Lot Release (only applicable for BLAs)

N/A

c) Facilities review/inspection

There were no facility changes in this submission.

d) Environmental Assessment

The submission included a request for a categorical exclusion from Environmental Assessment under 21 CFR § 25.31(c). The FDA reviewed and accepted this request. The applicant also claimed that to their knowledge, no extraordinary circumstances exist.

e) Product Comparability

N/A

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No nonclinical pharmacology/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/PHARMACOVIGILANCE

a) Clinical Program

To support extending the use of GARDASIL 9 indication to men and women 27 through 45 years of age, the Applicant refers to previously-reviewed results of base study, V501-019, and provides results from its the long-term follow-up (LTFU) (study, V501-019-21) of base study participants. The applicant also references study V501-108, conducted by an independent investigator, to support the use of GARDASIL 9 in men 27 through 45 years of age application.

Bioresearch Monitoring (BIMO) inspections of two clinical sites did not identify substantive problems that would impact the integrity and quality of data submitted in the application.

Design of Study V501-019

Study V501-019 was a 4-year long randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, immunogenicity, and safety of GARDASIL in 3,817 women 24 through 45 years of age. Women were screened on Day 1 and randomized 1:1 to receive GARDASIL (Types 6/11/16/18 VLPs with AAHS adjuvant) or placebo (AAHS adjuvant in saline) on Day 1, Month 2 and Month 6. During the base study, participants had regular gynecologic exams, provided specimens for HPV PCR and Pap testing, and provided sera for immunogenicity screening. To monitor safety, participants recorded temperatures for 4 days post-vaccination and injection-site and systemic adverse events (AE) for 14 days post-vaccination. Safety assessments were performed at each study visit, which occurred approximately every 6 months for the duration of the study.

The primary efficacy objective for V501-019 was to demonstrate that administration of GARDASIL reduces the combined incidence of HPV 6/11/16/18-related persistent infection and disease, compared to placebo, in women who were naïve to the relevant HPV type.

Design of Extension Studies V501-019-10 and V501-019-21

There were two extensions to the base study. The purpose of the first extension, V501-019-10, was to offer GARDASIL to women who had received placebo in the base study. Women who received GARDASIL in the base study are referred to as the early vaccination group (EVG), and women who initially received placebo and were then vaccinated in V501-019-10 are referred to as the catch-up vaccination group (CVG). These group designations become relevant in analyzing results of the second extension study, V501-019-21, which was an open-label, single arm, LTFU study in which 1336 women 24 through 45 years of age who were enrolled in the base study at five clinical sites in Colombia were followed for up to 10 years from enrollment in the base study. Of these, 1189 were 27 through 45 years of age when they received the first dose of vaccine (600 in the EVG and 589 in the CVG). No vaccine was administered during the LTFU phase. There were 3 study visits at years 6, 8, and 10. The median follow-up post-dose 3 for the EVG was 8.9 years (total 3,518 person-years) and for the CVG was 4.0 years (2,323 person-years). Efficacy could not be evaluated in the LTFU phase due to lack of a control arm. Therefore, the primary effectiveness endpoint was the cumulative incidence probability of HPV 6/11/16/18-related condyloma (genital warts) and CIN (any grade) at 10 years for the EVG and at 5 years for the CVG.

The primary effectiveness population was in the EVG cohort, which had longer post-vaccination follow-up than the CVG. The per-protocol effectiveness population (PPE) for the EVG cohort was defined as participants who received 3 vaccinations within one year of enrollment, did not have major deviations from the study protocol, were naïve to the relevant HPV types being analyzed prior to dose one, and remained PCR negative to the relevant HPV type through one month post-dose 3. There was no PPE for the CVG cohort, as baseline HPV status prior to vaccination was not established for this cohort. Other analysis populations consisted of women who received at least one vaccine dose and were naïve (by PCR of cervical swab and serology) to the vaccine HPV type being analyzed prior to dose one (i.e., HPV naïve to relevant type (HNRT)), and of women who received at least one dose of vaccine (i.e., Full Analysis Set (FAS)). The effectiveness of GARDASIL was evaluated using cohort-specific (i.e., EVG and CVG) incidences of CIN and condyloma during the single-arm LTFU, compared to incidences of cases that occurred during the AAHS-controlled base study.

Results of Base study V501-019, and LTFU study V501-019-21

In the base study, with a median duration of follow-up post-dose 3 of 3.5 years, the efficacy estimate against the combined endpoint of HPV 6-, 11-, 16-, and 18-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, cervical dysplasia (any grade CIN), AIS, and cervical cancer for women 27 through 45 years of age in the PPE population was 87.7% (95% CI: 74.5.%, 94.6%). In the same population, the efficacy of GARDASIL against the combined incidence of HPV 6-, 11-, 16-, and 18-related genital warts or cervical dysplasia was 95.0% (95% CI: 68.7%, 99.9%)

The base study, V501-019, was reviewed under STN 125126/773 in 2010. Although the pre-specified primary composite efficacy endpoint was met, the CBER clinical reviewer noted, in analyses of the full-analysis (FAS) population, that there were more cases of CIN2+ due to 10 non-vaccine oncogenic HPV types in the vaccine group (n=28) than in placebo group (n=20). The reviewer considered the most likely explanation for this finding to be a substantial imbalance in pre-existing non-vaccine type HPV infection after randomization at baseline (25 cases were PCR positive for a non-vaccine HPV type on Day 1 in the Gardasil group compared with 17 cases in the control group). However, based on the uncertainty regarding this risk, CBER agreed with the applicant's decision to withdraw the proposal under STN 125126/773 to extend the use of GARDASIL to include women up to 45 years of age. Instead, at the time, the GARDASIL package insert was revised to include data from V501-019 in order to inform patients and practitioners regarding the use of GARDASIL in women 27 through 45 years of age. Data from the LTFU study adequately address the remaining uncertainty regarding this risk signal (see below).

In the LTFU study, effectiveness was assessed in terms of the incidence of HPV-related condyloma and CIN (any grade). In the EVG, the cumulative incidence of HPV 6/11/16/18 related CIN and condyloma through Year 10 (number of cases/n individuals in the relevant analysis population) was 0.0006, 0.0024, and 0.0220 in the PPE, HNRT, and FAS populations, respectively. In the HNRT population, there were 4 cases of vaccine-type CIN observed during the base study and no new cases observed during the LTFU study. In the FAS population, following the 36 cases of vaccine type HPV-related endpoints that occurred during the base study, there was one case of vaccine-type disease of 16-related CIN 2/3 that occurred at Year 8 in a woman who was HPV 16+ by DNA at Day 1 and remained positive during the base study. These data support the duration of protection conferred by GARDASIL against genital warts and CIN (any grade) due to vaccine-type (6/11/16/18) HPV disease in women 27 through 45 years of age.

The data from the LTFU study are also notable because there were very few cases of non-vaccine type-related CIN 2+ cases detected in the FAS populations for both the EVG (n=1) during follow-up between Years 6 and 10 and the CVG (n=2) during follow-up between Years 1 and 4 after receiving a 3-dose regimen of GARDASIL. If the apparent increased risk for non-vaccine type CIN 2+ in the FAS noted in the base study was caused by the vaccine, many more cases of non-vaccine type-related disease should have been observed in both groups in the LTFU study, particularly in the CVG cohort. These data from the LTFU study provide clear evidence of benefit in preventing HPV disease over several years, regardless of HPV type, and allay concerns regarding the base study findings.

Effectiveness in women 27 through 45 years of age for the additional 5 HPV types in GARDASIL 9 is extrapolated based on clinical efficacy data from women 16 through 26 years of age (V503-001). The rationale for extrapolation includes the following considerations: 1) efficacy and effectiveness of GARDASIL are relevant to GARDASIL 9 since the vaccines are manufactured similarly and contain four of the same HPV L1

VLPs; and 2) similar to the findings in younger women 16 through 26 years of age, results from the PPE population of women in the base study demonstrate that GARDASIL is highly efficacious in the prevention of vaccine-type HPV persistent infection, genital warts, and cervical dysplasia (88.7%, 95%CI: [78.0, 95.0]), which supports similarity of performance of the vaccines across the two age cohorts.

Study V501-108

Study V501-108, conducted by an independent investigator, evaluated the safety and immunogenicity of a three-dose regimen of GARDASIL in 150 men 27 through 45 years of age. Men were administered vaccine at day 1, month 2, and month 6. Sera were collected at day 1 (pre-vaccination) and month 7 (one month post-dose 3) and tested for antibody to HPV 6, 11, 16, and 18. The seropositivity rate at month 7 was 100%. Merck compared month 7 GMTs from study V501-108 to those from an earlier study, V501-020 (reviewed by CBER under STN 125126/1895), of 16- through 26-year-old men in which the efficacy of GARDASIL was demonstrated. GMT ratios (V501-108/V501-020) for HPV 6, 11, 16, and 18 were 0.82 (95%CI: 0.65, 1.03), 0.79 (95%CI: 0.66, 0.93), 0.91 (95%CI: 0.72, 1.13), and 0.74 (95%CI: 0.59, 0.92), respectively. Effectiveness of GARDASIL 9 in men 27 through 45 years of age for the 4 HPV types common to GARDASIL and GARDASIL 9 was inferred based on these immunogenicity analyses. Effectiveness in males in this age group for the additional 5 HPV types in Gardasil 9 is extrapolated based on considerations similar to those described above with respect to females.

Statistical

CBER analyses of the effectiveness, immunogenicity, and safety data from the LTFU study were consistent with the stated conclusions from the CSR and Merck's statistical report submitted to STN 125508/493.

Pharmacovigilance

This application proposes to extend the current indications of GARDASIL 9 to include a new population: individuals 27 through 45 years of age. Merck's postmarketing plans for the new population include 3 components: (1) adding individuals 27 through 45 years of age to routine surveillance activities that are currently in place for GARDASIL 9, (2) completing an ongoing study of immunogenicity and safety of GARDASIL 9 in women 16 through 45 years of age, and (3) including women 27 through 45 years of age in the ongoing pregnancy registry, which collects pregnancy outcomes for women vaccinated with GARDASIL and GARDASIL 9 while pregnant.

CBER reviewed Merck's pharmacovigilance plan (PVP) for GARDASIL 9, with separate consideration of three specific subsets of the new population (27- through 45-year-old women, pregnant 27- through 45-year-old women, and 27- through 45-year-old men), and found Merck's PVP to be adequate.

b) Pediatrics

GARDASIL 9 has been adequately studied in the pediatric population. A partial waiver from assessments in children 0 through 8 years of age was granted in 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 the submission of this supplemental application.

c) Other Special Populations

N/A

7. SAFETY

Unsolicited adverse events (AEs), serious adverse events (SAEs), new medical conditions, and deaths were monitored for a total of 10 years in the studies of GARDASIL in women 27 through 45 years of age (studies V501-019 and V501-019-21). Solicited AEs were not collected due to the extensive safety database of GARDASIL in younger age groups. The safety profile of GARDASIL in 24- through 45-year-old women was not notably different from what has been characterized in younger women. Based on safety data for GARDASIL and GARDASIL 9 in women 16 through 26 years of age (study V503-001, reviewed under STN 125508/0), the only difference anticipated is slightly higher rates of local reactogenicity with GARDASIL 9 compared with GARDASIL. Therefore, the safety of GARDASIL 9 for women and men 27 through 45 years of age can be extrapolated from cross-study comparisons in younger ages and across GARDASIL and GARDASIL 9 formulations.

8. ADVISORY COMMITTEE MEETING

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting because review of this supplemental application 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 applicant submitted a patient package insert (PPI) and a package insert (PI) with proposed changes related to increasing to 45 years of age the upper age limit of individuals for whom the vaccine is indicated for use. Both documents were evaluated by a reviewer in the Advertising and Promotional Labeling Branch (APLB), and all committee members contributed to internal discussions regarding the labeling. The only substantive change made to the PPI was to replace “26” with “45” throughout as the upper age limit for use. A similar change was made in the PI. The PI was also revised to include a description of the studies upon which the extension of the population to receive GARDASIL 9 was based. The most substantive change made to the originally

proposed PI was to add information regarding the study in men 27 through 45 years of age (study V501-108). Merck viewed the results from study V501-108 as supportive of the data in the LTFU study but did not propose reference to the study in the PI. CBER asked that the PI include V501-108 study information, and Merck agreed. Other minor revisions were made to the PI in a short series of communications between Merck and CBER. CBER agreed to the PI submitted to the file on September 28, 2018.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The committee recommends approval of this supplement to extend the indication for GARDASIL 9 to include use in individuals 27 through 45 years of age.

b) Risk/ Benefit Assessment

HPV infection is nearly universal in sexually active populations, and can lead to life-threatening (cervical, vulvar, vaginal, and anal cancers) and serious conditions (cervical dysplasia, genital warts). Published data indicate that 27- through 45-year-old women and men acquire new HPV infections and that most have not been exposed to all 9 HPV types covered by GARDASIL 9.

In previously-reviewed data from the placebo-controlled base study (V501-019), efficacy of GARDASIL was demonstrated for vaccine type HPV infection and disease in women 27 through 45 years of age. Results of V501-019 and its long-term follow-up studies further support the effectiveness of GARDASIL and the duration of protection in this population. Based on the long-term follow-up data in both the early vaccination and the catch-up vaccination groups, the previous uncertainty with respect to risk of non-vaccine type related HPV disease has been resolved. In addition, because of the 5 additional oncogenic HPV types covered by GARDASIL 9 (which account for most of the HPV-related disease not caused by the 4 HPV types covered by GARDASIL), it is reasonable to conclude that any remaining theoretical risk of non-vaccine-type related HPV disease will be lower with GARDASIL 9 than with GARDASIL. Furthermore, it is reasonable to anticipate that the clinical benefit for GARDASIL 9 will be greater than or equal to that observed with GARDASIL in older adults.

Given that the most substantial risks of vaccination with GARDASIL 9 are injection site reactions that are self-limited and mild in severity, the potential benefits of the vaccine, which can prevent serious and/or life-threatening disease, outweigh the potential risks. Therefore, the overall benefit-risk assessment is favorable for use of GARDASIL 9 in adults 27 through 45 years of age.

c) Recommendation for Postmarketing Activities

The Applicant's proposed PVP is adequate.