

Summary Basis for Regulatory Action

Date: December 9, 2014
From: Haruhiko Murata, Chair of the Review Committee
BLA/ STN#: 125508/0

Applicant Name: Merck Sharpe & Dohme Corp.

Date of Submission: December 10, 2013
PDUFA Goal Date: December 10, 2014

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

Indication:

GARDASIL 9 is indicated for the prevention of the following:

For females aged 9 to 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.
- 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 males aged 9 to 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.

Recommended Action: Approval

Signatory Authorities Action: Approval

Office Signatory Authority: Marion Gruber, Ph.D., Director, Office of Vaccines 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.

Specific Documentation Used in Developing the SBRA	Reviewer Name
Clinical Review	Sixun Yang, M.D., Ph.D.
Pharmacovigilance Review	Adamma Mba-Jones, M.D., M.P.H.
Statistical Review	Lihan Yan, Ph.D.
CMC Review	Haruhiko Murata, M.D., Ph.D.
Testing Method and Analytical Chemistry	Freyja Lynn, Ph.D. Leslie Wagner, Ph.D. Lokesh Bhattacharya, Ph.D. Karen Campbell, M.S. Anil Choudhary, Ph.D. Muhammad Shahabuddin, Ph.D. Claire Wernly, Ph.D. Noel Baichoo, Ph.D.
Pharmacology/ Toxicology Review	Nabil Al-Humadi, Ph.D.
Facilities	Jeremy Wally, Ph.D.
Bioresearch Monitoring Review	Erin McDowell
Labeling	Dana Martin Daphne Stewart Sixun Yang, M.D., Ph.D.; Nancy Miller, M.D.; Lihan Yan, Ph.D.; Adamma Mba-Jones, M.D., M.P.H.; Haruhiko Murata, M.D., Ph.D.; Laura Montague; Bharat Khurana, D.V.M., Ph.D.
Proprietary Name	Dana Martin

1. Introduction

Merck Sharp & Dohme Corp. submitted Biologics License Application (BLA) 125508 on December 10, 2013 to seek licensure of a Human Papillomavirus (HPV) 9-valent Vaccine, Recombinant (covering HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58). The proprietary name for this vaccine is GARDASIL 9. Merck is currently licensed to manufacture and market the quadrivalent HPV vaccine GARDASIL (covering HPV types 6, 11, 16, and 18); thus, GARDASIL 9 is the applicant's second generation HPV vaccine. GARDASIL 9 is indicated for the prevention of diseases (cervical, vulvar, vaginal, and anal cancer and associated pre-malignant lesions; genital warts) caused by HPV types covered by the vaccine for girls and women 9-26 years of age and boys 9-15 years of age. GARDASIL 9 is a sterile liquid suspension consisting of recombinant, purified virus-like particles (VLPs) formed by the HPV L1 major capsid protein. The L1 capsid protein for each HPV type present in the vaccine is produced independently in the yeast *Saccharomyces cerevisiae*. The expressed L1 protein is purified and adsorbed on an aluminum adjuvant (amorphous aluminum hydroxyphosphate sulfate, or AAHS). GARDASIL 9 does not contain preservatives or antibiotics. GARDASIL 9 is available in single-dose vial and single-dose prefilled syringe presentations and is intended for intramuscular injection (0.5 mL/dose) on a three dose schedule (0-, 2-, and 6-months).

2. Background

HPV infections cause benign and malignant dysplastic diseases, localized primarily in the anogenital area, in both men and women. Chronic HPV infection significantly increases the risk of cervical and other anogenital cancers. Cervical cancer is the second most common cancer in women worldwide, associated with approximately 530,000 incident cases and 275,000 deaths each year. Overall, HPV is responsible for approximately 5% of the global cancer burden. Nearly 100% of cervical cancers and 90% of anal cancers are caused by oncogenic HPV types. Approximately 70% of cervical cancers and 90% of anal cancers are caused by HPV types 16 and 18, both of which are targeted by the currently licensed HPV vaccines, GARDASIL (quadrivalent; HPV types 6, 11, 16, and 18) and Cervarix (bivalent; HPV types 16 and 18). However, both GARDASIL and Cervarix do not provide effective cross-protection against other oncogenic HPV types. There is an unmet medical need for a vaccine that prevents anogenital cancers caused by HPV types other than HPV 16 and 18. GARDASIL 9 targets five additional oncogenic HPV types (31, 33, 45, 52, and 58) that together cause approximately 20% of cervical cancers. Thus, GARDASIL 9 has an estimated potential to prevent 90% of anogenital cancers caused by HPV.

Data to support this BLA were generated in studies conducted under IND 13447 (established in August 2007). At the End-of-Phase 2 Meeting (September 2008), CBER agreed that the labeled indication for GARDASIL 9 would be based on (1) demonstration of clinical efficacy against persistent infection and a composite disease endpoint caused by the five new HPV types (31, 33,

45, 52, and 58), and (2) non-inferior immunogenicity for the four original HPV types (6, 11, 16, and 18).

Merck seeks licensure of GARDASIL 9 for prevention of the following:

For females aged 9 to 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.
- 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 males aged 9 to 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.

A 0.5 mL dose of GARDASIL 9 contains the following:

GARDASIL 9 Drug Product Composition

Component	Quantity per 0.5-mL Dose	Function
HPV Type 6 L1 Protein	30 µg	Immunogen
HPV Type 11 L1 Protein	40 µg	Immunogen
HPV Type 16 L1 Protein	60 µg	Immunogen
HPV Type 18 L1 Protein	40 µg	Immunogen
HPV Type 31 L1 Protein	20 µg	Immunogen
HPV Type 33 L1 Protein	20 µg	Immunogen
HPV Type 45 L1 Protein	20 µg	Immunogen
HPV Type 52 L1 Protein	20 µg	Immunogen
HPV Type 58 L1 Protein	20 µg	Immunogen
Amorphous aluminum hydroxyphosphate sulfate adjuvant	500 µg (aluminum content)	Adjuvant
Sodium Chloride	9.56 mg	---(b)(4)---
L-Histidine	0.78 mg	--b)(4)-
Polysorbate 80	50 µg	---(b)(4)---
Sodium Borate	35 µg	-(b)(4)-
Water for Injection	QS	Solvent

Thus, compared with GARDASIL, GARDASIL 9 contains 2.25-fold more total protein antigen (270 µg vs. 120 µg) and 2.22-fold more aluminum adjuvant (500 µg vs. 225 µg).

Testing and acceptance criteria for release and stability of drug substance (b)(4) are shown in the following table:

Testing and Acceptance Criteria for Release and Stability of Drug Substance

(b)(4)	
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Testing and acceptance criteria for release and stability of final container drug product are shown in the following table:

Testing and Acceptance Criteria for Release and Stability of Final Container Drug Product

Test	Acceptance Criteria for Release	Acceptance Criteria for Stability
<p>----(b)(4)---- ----- Potency --(b)(4)-- Lower Limits</p>	<p>----- ----- ----- ----- ----- ----- ----- ----- ----- -----</p>	<p>----- ----- ----- ----- ----- ----- ----- ----- ----- -----</p>
<p>----(b)(4)---- ----- Potency --(b)(4)-- Upper Limits</p>	<p>----- ----- ----- ----- ----- ----- ----- ----- ----- -----</p>	<p>(b)(4)</p>
Identity	Conforms	N/A
Sterility	No growth	No growth
Endotoxin	---(b)(4)---	(b)(4)
Aluminum	---(b)(4)---	(b)(4)
(b)(4)	---(b)(4)---	(b)(4)
Characteristics	White, cloudy liquid	White, cloudy liquid
----- ----- (b)(4)	(b)(4)	-(b)(4)-
Package Identity	Label checks of finished market package confirmed; White, cloudy liquid per Characteristics, and Conforms to specifications in the method (Identity)	N/A
Volume of Fill	----- ----- ----- ----- ----- ----- ----- ----- ----- -----	(b)(4)
Syringeability (Syringe Only)	----- ----- ----- ----- ----- ----- ----- ----- ----- -----	----- ----- ----- ----- ----- ----- ----- ----- ----- -----

Many aspects of manufacturing for GARDASIL 9 remain the same relative to GARDASIL. The two facilities proposed for the manufacture of GARDASIL 9 (----- (b)(4) -----) are

GARDASIL 9 received a pregnancy Category B designation, which will be reflected in the Prescribing Information for GARDASIL 9 under Section 8.1 Pregnancy.

5. Clinical Pharmacology

No clinical pharmacology or pharmacokinetic studies were performed in the clinical development program for GARDASIL 9.

Efficacy of GARDASIL 9 against anogenital diseases related to the vaccine HPV types in humans is thought to be mediated by antibody responses induced by the vaccine, although the exact mechanism of protection is unknown.

6. Clinical Effectiveness

a) Clinical Program

Merck submitted six final study reports of clinical trials in support of this BLA:

- Study V503-001 was a pivotal efficacy study conducted in women 16 to 26 years of age.
- Study V503-002 was a pivotal immunological bridging study to bridge clinical efficacy obtained from Study V503-001 to boys and girls 9 to 15 years of age; the immunobridging approach was necessary because performing genital examination in this younger population was not feasible.
- Study V503-009 provided additional immunological bridging from GARDASIL to GARDASIL 9, in females 9 to 15 years of age, by demonstrating that both vaccines have similar immunogenicity with respect to HPV types 6, 11, 16, and 18.
- Study V503-005 evaluated potential interference of GARDASIL 9 with Menactra [Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] when administered concomitantly to children 11 to 15 years of age.
- Study V503-006 evaluated the safety and immunogenicity of GARDASIL 9 in subjects who were previously vaccinated with GARDASIL.
- Study V503-007 was a concomitant administration study with a non-US-licensed vaccine (Repevax) and provided additional safety data for GARDASIL 9 in adolescents 11 to 15 years of age.

The major findings of these studies are summarized below.

Study V503-001 was a randomized, double-blinded, controlled (*vs.* GARDASIL), Phase 2b/3 trial to evaluate the efficacy, immunogenicity, and safety of GARDASIL 9 in women 16 to 26 years of age. Part A (Phase 2b) was a dose-finding study, and Part B (Phase 3) was an efficacy and safety study. Part B also included those subjects enrolled under Part A who received the dose formulation of GARDASIL 9 selected for Part B or the GARDASIL control dose. The study randomized 14,215 women 16 to 26 years of age (from 5 continents and 18 countries) into two treatment groups: 7,106 GARDASIL 9 recipients and 7,109 GARDASIL recipients. Both

vaccines were administered intramuscularly (IM) at Day 1, Month 2, and Month 6. The median duration of follow-up post-Day 1 was approximately 40 months. As agreed to in pre-licensure discussions with CBER, effectiveness of GARDASIL 9 with respect to the original HPV types (6, 11, 16, and 18) was inferred by immunobridging from GARDASIL to GARDASIL 9 via non-inferior immunogenicity comparison, and the prophylactic efficacy for the new HPV types was based on combined incidence of CIN 2/3, VIN 2/3, and VaIN 2/3 or worse related to HPV types 31, 33, 45, 52, and 58. Since efficacy evaluation of anal lesions associated with the five new HPV types was not feasible due to low incidence, CBER agreed that effectiveness with respect to this endpoint could be inferred from efficacy against genital lesions (on the basis of highly similar pathophysiology), immunogenicity, and prevention of persistent infection. Safety endpoints included injection site and systemic reactions, new onset of medical conditions including potential autoimmune disorders, and serious adverse events (SAEs).

The immunogenicity results for study V503-001 showed that GMT responses for each of the original HPV types induced by GARDASIL 9 in females 16 to 26 years of age were non-inferior compared with the GARDASIL group at 4 weeks post-dose 3 in the per protocol immunogenicity (PPI) population. Numerically, the GMT ratios (GARDASIL 9/GARDASIL) for HPV types 6, 11, 16, and 18 ranged from 0.80 to 1.19 with lower bounds of 95% confidence intervals (CIs) all above 0.67, the pre-specified success criterion. The proportion of subjects who became seropositive to HPV types 6, 11, 16, and 18 by Month 7 in the GARDASIL 9 group was also non-inferior to that in the GARDASIL group. Therefore, non-inferior immunogenicity supports bridging prior efficacy findings for GARDASIL to GARDASIL 9 with respect to persistent infection related to HPV types 6/11/16/18 as well as anogenital disease.

The V503-001 primary efficacy endpoint for the new HPV types was assessed in the per protocol efficacy (PPE) population. The overall observed efficacy against HPV 31/33/45/52/58-related high-grade cervical, vulvar, and vaginal lesions in females 16 to 26 years of age in the PPE population was 96.7% (95% CI: 80.9, 99.8). The results met the success criterion for this efficacy endpoint (the lower bound of the two-sided 95% CI greater than 25%). The efficacy of GARDASIL 9 in preventing high grade genital lesions was consistent (ranging from approximately 87% to 100%) among different subgroups in terms of age, race, geographic region, ethnicity, hormone contraception use, and lifetime number of sexual partners. GARDASIL 9 was also efficacious in preventing HPV 31/33/45/52/58-related persistent infection (≥ 6 months as well as ≥ 12 months). In addition, GARDASIL 9 was also efficacious in reducing the incidence of HPV 31/33/45/52/58-related genital biopsy and definitive therapy by 31.3% and 46.5%, respectively.

Study V503-002 was an open label, multi-centered study to assess immunogenicity, safety, and manufacturing consistency of GARDASIL 9. The study enrolled 2604 children 9 to 15 years of age (1935 girls and 669 boys) and 470 young women 16 to 26 years of age. The results showed that antibody GMTs for each of the GARDASIL 9 vaccine HPV types were non-inferior (and numerically higher) in children compared with young women, with GMT ratios (children/women) at 4 weeks post-dose 3 ranging from 1.83 to 3.3. These results support the bridging of efficacy findings in women (16 to 26 years of age) to children (9 to 15 years of age). The GMT responses for each of the nine HPV types at 4 weeks post-dose 3 were similar among

girls (9 to 15 years of age) randomized to one of three Final Manufacturing Process vaccine lots and met the success criteria for clinical demonstration of lot consistency.

The immunogenicity of GARDASIL 9 was non-inferior to GARDASIL with respect to the original HPV types in girls 9 to 15 years of age as shown in study V503-009, further supporting the bridging of efficacy of between GARDASIL 9 and GARDASIL for this age group.

Concomitant administration of GARDASIL 9 with the vaccines Menactra and Adacel did not show any adverse impact on immune responses to the antigen components in GARDASIL 9, Menactra, or Adacel (study V503-005).

When GARDASIL 9 was administered to subjects who were previously vaccinated with a 3-dose regimen of GARDASIL (study V503-006), seroconversion rates for all nine HPV types were greater than 98% at 4 weeks after the third dose of GARDASIL 9. Antibody GMTs for the five new HPV types (31/33/45/52/58) were lower than those in HPV vaccine naïve subjects in the other studies. The clinical significance of this finding is unclear.

Bioresearch Monitoring (BIMO) Inspections

BIMO inspections of six clinical sites (four US sites and Bangkok, Thailand and Frederiksberg, Denmark) were conducted in support of this BLA; these clinical sites were involved in studies V503-001 and V503-002. Inspections of these clinical sites did not reveal significant problems that impact the data submitted in this BLA.

The Bioresearch Monitoring Branch received (b)(3)(b)(4)(b)(7) complaint on (b)(3)(b)(4)(b)(7) regarding possible Good Clinical Practice (GCP) noncompliance at the V503-002 study sites in (b)(3)(b)(4)(b)(7). The complaint alleged issues with obtaining proper informed consent and providing adequate medical monitoring and follow-up. After receiving responses from Merck following an Information Request regarding this matter, significant issues were identified at the sites in -----
----- (b)(3)(b)(4)(b)(7) ----- of subjects enrolled in study V503-002). After reviewing Merck's clinical site monitoring reports, copies of the informed consent documents, and data obtained through the Vaccination Report Cards (VRCs), the review committee concluded that significant GCP noncompliance may have occurred; thus, a decision was made to exclude data from sites (b)(3)(b)(4)(b)(7) for the purpose of informing regulatory action. Data exclusion was found to have minimal impact on the immunogenicity analysis of study V503-002 and overall safety analyses.

b) Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), this BLA was required to contain an assessment of the safety and effectiveness of the product for the claimed indications in all pediatric age groups. Merck has fulfilled the pediatric study requirement for children 9 to 16 years of age in this application. The applicant's request for a partial waiver for children from birth to less than 9 years of age was presented to the Pediatric Review Committee (PeRC) on July 23, 2014. CBER agreed to waive the pediatric study requirement for ages 0 through 8 years because initiating vaccination prior to age 9 does not represent a meaningful therapeutic benefit over

initiating vaccination at 9 years of age and older, and GARDASIL 9 is not likely to be used in a substantial number of children in this age group.

7. Safety

Safety findings were consistent among the six clinical studies. The safety profile of GARDASIL 9 was generally favorable. Vaccine-related systemic adverse reactions reported in the GARDASIL 9 treatment group were similar to those in the GARDASIL treatment group; however, the incidence of injection-site reactogenicity was numerically higher in the GARDASIL 9 group (90.2%) compared with the GARDASIL group (84.0%). The most common injection-site reactions were injection-site pain, swelling, and erythema. The incidence of injection-site reactions in children 9 to 15 years of age was numerically lower compared with females 16 to 26 years of age.

Concomitant administration of GARDASIL 9 with the vaccines Menactra and Adacel did not negatively impact the safety profile of GARDASIL 9. In addition, GARDASIL 9 was tolerated well in subjects who were previously vaccinated with GARDASIL.

New onset clinical conditions of potential autoimmune etiology were well-balanced between GARDASIL 9 and GARDASIL treatment groups except multiple sclerosis (MS); there were 5 cases of MS in the GARDASIL 9 group compared with 2 cases in the GARDASIL group. The clinical significance of this apparent imbalance is unclear due to the small case numbers involved. The incidence rate of MS in the GARDASIL 9 group is within the limits of the population background. Post-marketing assessment for immune-mediated medical conditions will be conducted using the FDA Mini-Sentinel surveillance system.

In clinical studies, 1,178 (86%) and 1,108 (85%) pregnancies with known outcomes occurred in subjects vaccinated with GARDASIL 9 and GARDASIL, respectively. Of these, 98% occurred in the clinical efficacy study (V503-001). Data assessed over the entire follow-up period did not reveal an increased risk of adverse pregnancy outcomes in subjects receiving GARDASIL 9 when compared with subjects receiving GARDASIL. Over the entire study period, the overall rates of spontaneous abortion (SA) in the GARDASIL 9 and GARDASIL groups were similar: 122/1,178 (10.4%) and 143/1,108 (12.9%) respectively. A *post-hoc* analysis of the GARDASIL 9 group showed that among 92 pregnancies with estimated date of conception within 30 days of vaccination, 17 of 89 (19.1%) with known outcome resulted in SA, compared with 105 of 1,089 (9.6%) with known outcome among 1,281 pregnancies with estimated date of conception not within 30 days of vaccination. A similar imbalance occurred for elective abortions (EA), with rates of 27/89 (30.3%) and 116/1,089 (10.7%), respectively, among pregnancies with known outcome and estimated date of conception either within or not within 30 days of vaccination. For the 89 pregnancies with estimated date of conception within 30 days of vaccination with GARDASIL, the rate of SA among pregnancies with known outcome was 7/88 (8.0%), which was lower than the corresponding rate for GARDASIL 9 ($p=0.04$). Further statistical analyses by review committee members included assessment of multiple potential confounders, such as age, race, geographical region, smoking status, previous history of SA, concomitant medication

use, and history of chlamydia, after which the imbalance in SA between the two treatment groups persisted.

Merck's explanations of the apparent imbalance in SA for the GARDASIL 9 clinical studies include the following: (1) analyses of SA are *post-hoc* involving relatively small case numbers; (2) possibility of the SA rate in the GARDASIL control group being unexpectedly low due to chance; (3) possible misclassification of elective abortions as SA for certain cases, especially those from Latin American countries; (4) imprecision in the assessment of the date of last menstrual period, which may have yielded inexact time windows; (5) observed SA rates in the clinical studies were within background rates reported in the general population. Imbalances in SA to this extent against the placebo group were not observed in clinical studies supporting licensure of GARDASIL. However, the review team noted that in clinical studies supporting licensure of Cervarix (bivalent; HPV types 16 and 18; adjuvanted with AS04, consisting of aluminum hydroxide and monophosphoryl lipid A), a similar imbalance was observed in SA rates among pregnancies occurring -30 days to +40 days around the time of vaccination (13.8% for the Cervarix group vs. 9.8% for the control group).

These apparent imbalances in SA were discussed on numerous occasions within the review committee and in conjunction with management for the Office of Vaccines Research and Review (OVRR) and the Office of Biostatistics and Epidemiology (OBE). The reasons for the apparent imbalances are unknown. Considerations included that the apparent imbalances may be due solely to chance, may result from undiscovered confounding variables, or may signal a true risk. Spontaneous abortions and other pregnancy-related outcome data for GARDASIL 9 will be collected through a post-marketing pregnancy registry conducted by Merck (using the same methodology as the pregnancy registry for GARDASIL). In addition, a post-marketing targeted observational study through the Vaccine Safety Datalink (VSD) administered by the Centers for Disease Control and Prevention (CDC) is being considered. Consultations are ongoing between CBER and CDC on a VSD study protocol for assessing SA in recipients of GARDASIL 9.

8. Advisory Committee Meeting

CBER did not convene an Advisory Committee meeting to discuss licensure of GARDASIL 9. Information submitted in this BLA did not raise significant concerns or controversial issues that would have benefitted from discussion with an Advisory Committee.

9. Other Relevant Regulatory Issues

N/A

10. Labeling

The proprietary name GARDASIL 9 was reviewed by the Advertising and Promotional Labeling Branch (APLB; CBER) and found to be acceptable.

The carton/container labels as well as the package insert and patient information were reviewed by all relevant review committee members, including clinical, statistical, pharmacovigilance, product, and APLB reviewers. All issues, including required revisions, were satisfactorily resolved following discussions with the applicant.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

Based on review of all supportive clinical and product data, the review committee recommends approval of this BLA for the proposed indications.

b) Risk/ Benefit Assessment

The submitted data support the effectiveness of GARDASIL 9 in males 9 to 15 years of age and females 9 to 26 years of age in preventing benign and malignant anogenital lesions caused by the vaccine HPV types as described in the proposed indications. The safety profile of GARDASIL 9 observed in the clinical trials was favorable and similar to the licensed GARDASIL vaccine. Injection-site reactions (swelling, pain, and erythema) represented the most commonly reported adverse events in clinical trial subjects. Potential safety concerns can be adequately addressed in post-licensure activities. The review committee concluded that the clinical benefits of GARDASIL 9 outweigh its risks for the indicated population.

c) Recommendation for Post-marketing Risk Management Activities

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

d) Recommendation for Post-marketing Activities

Consultations with the Centers for Disease Control and Prevention (CDC) to evaluate spontaneous abortion after GARDASIL 9 vaccination in early pregnancy using the Vaccine Safety Datalink (VSD) are in progress.

There are no post-marketing requirements under Section 505B(a) of the Food, Drug, and Cosmetic Act.

The following post-marketing activities are included in the approval letter:

Post-marketing Studies Subject to Reporting Requirements of 21 CFR 601.70:

1. To complete the ongoing 10-year study extension of Protocol V503-002 to evaluate the long-term safety, immunogenicity and effectiveness of Gardasil 9 in males and females who were between 9 and 15 years of age at enrollment.

Study Completion: September 30, 2022

Final Report Submission: March 31, 2023

2. To conduct a 10-year study extension of Protocol V503-001 to evaluate the long-term safety, immunogenicity and effectiveness of Gardasil 9 in women who were 16 to 26 years of age at enrollment.

Final Protocol Submission: January 31, 2015

Study Completion: June 30, 2026

Final Report Submission: December 31, 2026

3. To conduct an observational study to further characterize the safety profile of Gardasil 9 in approximately 10,000 persons.

Final Protocol Submission: December 31, 2015

Study Completion: December 31, 2018

Final Study Report Submission: December 31, 2019

4. To establish a pregnancy registry as described in the applicant's final protocol submitted September 16, 2014, to continue for at least 5 years, to prospectively collect data on spontaneously reported exposures to Gardasil 9 within 30 days prior to the last menstrual period or at any time during pregnancy. The applicant will submit annual reports as well as a five-year summary report, after which the applicant will continue enrolling patients in the registry pending CBER review of the report and determination of whether the registry can be discontinued.

Establishment of Pregnancy Registry: January 31, 2015

Five-Year Summary Report Submission: August 10, 2020

Final Report Submission: 18 months after enrollment of the last patient