Summary Basis for Regulatory Action

Date: June 9, 2010

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

BLA/ STN#: 125126/1516

Applicant Name: Merck & Co.

Date of Submission: May 11, 2009

PDUFA Goal Date: June 10, 2010

Proprietary Name/ Established Name: GARDASIL®

Primary Change to the Gardasil Package Insert Sought Under This BLA Supplement: In the Highlights Section, under "**Drug Interactions**", the applicant proposed the following change:

from:

"*GARDASIL may be administered concomitantly with RECOMBIVAX HB.*"

to:

"*GARDASIL may be administered concomitantly with RECOMBIVAX HB or with Menactra and Adacel*."

Recommended Action: Approval

Signatory Authorities Action: Approval

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

√ **I concur with the summary review.**

□ **I concur with the summary review and include a separate review to add further analysis.**

□ **I do not concur with the summary review and include a separate review.**

Table 1: Review documents used in compiling this SBRA:

Review Category	Reviewer
Clinical Review	Anuja Rastogi, M.D. Jeff Roberts, M.D.
Statistical Review	Martha Lee, Ph.D.
HPV Serology Assay Review	Haruhiko Murata, Ph.D.
Diphtheria/Tetanus Serology Assay Review	Leslie Wagner
Pertussis Serology Review	Drusilla Burns, Ph.D.
Neisseria Meningitidis Serology Assay Review	Margaret Bash, M.D., M.P.H.
Labeling Review	Lisa Stockbridge, Ph.D.
Bioresearch Monitoring Inspection Review	Lillian Ortega

1. Introduction

GARDASIL® is a non-infectious recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. It was licensed in the U.S. in June of 2006. At the time of licensure, a study of concomitant administration of Gardasil with Recombivax HB had been completed and reviewed, and the original label included approval of concomitant use.

On May 11, 2009, Merck submitted sBLA 125126/1516, which contained data to demonstrate safety and immunogenicity when Gardasil is administered concomitantly with Adacel and Menactra.

2. Chemistry Manufacturing and Controls (CMC) – Serology Assay Reviews

Full CMC review of Gardasil was completed at the time of original licensure in June 2006. All lots of vaccine used in the concomitant study were reviewed and released for distribution by CBER.

The CMC reviews focused on the assays used to evaluate the immune response to each of the antigens included in the vaccines administered in the study. Because assessment of potential diminution of the immune response was one of the primary goals of the study, validation of the serology assays was a critical and essential part of the review of this supplement.

The assays for the serological responses to 14 separate antigens were considered. Separate reviews were performed for the immune response assay for each of the following sets of antigens:

1. Gardasil: Antibody response to HPV VLP types 6, 11, 16, and 18 as measured by Merck's proprietary Competitive Luminex Immunoassay Version 2.0 (cLIA v2.0)
2. Menactra: Serum bactericidal assay (SBA) titer against *Neisseria meningitidis* serogroups A, C, W-135, and Y.

3. Adacel: Diphtheria -------(b)(4)---------- Assay titer and anti-tetanus ELISA titer
4. Adacel: ELISA titers against the following pertussis antigens: pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae (FIM)

In the case of each of the assays, the reviewer concluded that the data provided was adequately validated for the purpose of evaluating the concomitant administration of Gardasil with Menactra and Adacel.

3. Clinical

The study submitted in support of the application was a randomized, open label safety and immunogenicity trial of concomitant use of Gardasil with Adacel and Menactra in male and female adolescents aged 11-17 years. 1042 subjects were randomized 1:1 to the concomitant or non-concomitant (sequential) study group.

The Concomitant group on Day 1 received Gardasil in one limb, while also receiving separate injections of Menactra and Adacel in the opposite limb. The Non-concomitant group received Gardasil on Day 1 in one limb and then Menactra and Adacel, as separate injections, at Month 1 in the opposite limb. Subjects in both vaccination groups received the second dose of Gardasil at Month 2 and the third dose at Month 6.

All study sites were in the U.S. The race distribution of subjects in the clinical trial was as follows: 77.7% White; 6.8% Hispanic (Black and White); 12.3% Black; 1.4% Multi-racial; 1.2% Asian; 0.2% Indian; and 0.4% American Indian.

Immunogenicity endpoints included anti-VLP antibody titers against HPV types 6, 11, 16, and 18, serum bactericidal assay (SBA) titers against meningococcal serogroups A, C, Y, and W-135, diphtheria and tetanus ELISA titers and antibody titers against pertussis antigens PT, FHA, PRN and FIM.

Of note regarding the meningococcal SBA: The SBA utilizes complement with dilutions of test sera to determine the highest dilution that achieves at least 50% killing of the target strain for each meningococcal serogroup. For primary BLAs for new meningococcal vaccine products, CBER has requested that at least a subset of SBAs be performed using complement from a human source. After internal discussion, the review team agreed that the SBA data submitted here, which used complement from a baby rabbit source, was adequate for the intended purpose of evaluating concomitant administration.

The primary endpoints and the criteria by which non-inferiority was determined are displayed in Table 2 below. The primary endpoints for evaluation of Adacel and Menactra and their corresponding non-inferiority margins were pre-specified to be consistent with the pivotal licensure studies for these vaccines. More information on those pivotal studies is available in the Adacel and Menactra package inserts published on the FDA website here:
http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

Table 2: Gardasil, Adacel and Menactra Primary Endpoints and Non-Inferiority Criteria

Vaccine Component	Primary Endpoint	Non-inferiority Criteria
Tetanus **Diphtheria**	% of subjects with titers ≥ 0.1 IU/ml	The lower limit of 95% CI for the difference (concom group minus non-concom) group is > -10%.
Anti-PT **Anti-FHA** **Anti-PRN** **Anti-FIM**	GMT	The lower limit of 95% CI for GMT ratio (concom/non-concom) is >0.67
Serogroup A **Serogroup C** **Serogroup W-135** **Serogroup Y**	% of subjects with ≥ 4-fold rise in titer from pre- to post-vaccination.	The lower limit of 95% CI for the difference (concom group minus non-concom Group) is > -10%.
HPV 6 **HPV 11** **HPV 16** **HPV 18**	% of subjects with +SCR to vaccine HPV type	The lower limit of 95% CI for the difference (concom group minus non-concom) group is > -5%.
	GMT	The lower limit of 95% CI for GMT ratio (concom/non-concom) is >0.5

Immunogenicity

In the case of each of the 14 antigens in the 3 vaccines studied, the immune response after concomitant administration (Gardasil + Adacel + Menactra) was non-inferior to the immune response after non-concomitant (sequential) administration (Gardasil, followed by Adacel + Menactra) by the pre-specified statistical criteria displayed in Table 2.

Of note regarding the immune response analyses: Implicit in the design of the study was the assumption that there is no immune interaction between Menactra and Adacel when given together. No conclusions can be made regarding the potential immune interaction between Gardasil and Menactra or between Gardasil and Adacel.

Safety

The safety profile of concomitant versus non-concomitant administration was comparable. No clinically meaningful differences were noted between groups for systemic or injection-site adverse experiences.

Serious Clinical Adverse Experiences

There were two serious adverse experiences reported in the study. Both subjects were in the non-concomitant group. The first subject (b)(6) 52995'was a 12 year old male who had completed all vaccinations, including all 3 Gardasil vaccinations (Day 1, Month 2,

Month 6) as well as Menactra and Adacel vaccinations (Month 1). The day after his 3rd dose of Gardasil, the patient awoke with complaints of muscle weakness in his arms and legs, and a temperature of 101.3 F. The patient was taken to the emergency department by ambulance, where a neurological exam, blood tests, x-ray, and pulse oxymitery were documented to be normal. The patient was discharged in his normal state on the same day, without any needed interventions or further complications.

The second subject was (b)(6)53737 a 12 year old female with a pre-existing condition of salivary gland stones. She had a scheduled parotidectomy on Day 7 of the study, requiring overnight hospitalization. The patient recovered without incident.

Deaths
No deaths were documented during the clinical trial.

Pediatrics
The Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) is not applicable in the case of this efficacy supplement. No further concomitant administration pediatric studies will be required by the Agency at this time.

Clinical Reviewer Overall Conclusions
Data submitted to the BLA supplement demonstrate that the immune response after concomitant administration of Gardasil, Adacel, and Menactra is comparable to the immune response after non-concomitant administration. There is no evidence for immunogenicity interference.

The safety profile of the vaccines when given concomitantly or non-concomitantly is comparable.

4. Statistical

The statistical reviewer reached the following conclusions:

Results of the primary immunogenicity analyses performed in the per-protocol population show that non-inferiority for the following endpoints were demonstrated in the Concomitant Vaccination Group (receiving qHPV vaccine + Menactra and ADACEL) compared with the Non-Concomitant Vaccination Group (receiving first dose of GARDASIL on Day 1 and Menactra and ADACEL one month later):

- anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs at 4 weeks Postdose 3 and the percentage of subjects who seroconverted by 4 weeks Postdose 3 of GARDASIL,
- the proportion of subjects with a 4-fold or greater rise in titers for *Neisseria meningitidis* serogroups A, C, Y, and W-135 at one month post-vaccination with Menactra,
- the proportion of subjects with diphtheria and tetanus titers ≥0.1 IU/mL at 4 weeks post injection of Menactra + ADACEL, and

- GMTs developed for each pertussis component at 4 weeks post injection with ADACEL.

Safety data from Protocol 025 show that the concomitant administration of a first dose of GARDASIL with Menactra and ADACEL is generally well tolerated compared to when the first dose of GARDASIL vaccine is given separately from Menactra and ADACEL.

5. Bioresearch Monitoring

The bioresearch monitoring inspections of four clinical sites did not reveal problems that impact the data submitted in the application.

6. Labeling

The package insert (PI) was evaluated by a reviewer in the Advertising and Promotional Labeling Branch (APLB). In addition, each committee member contributed to internal discussions. The most substantial labeling issue was the level of detail with which to display the data in the label. The consensus on the review committee was that after specifying the design and conduct of the concomitant administration study, the immunogenicity non-inferiority data and the safety data should be broadly summarized in prose.

After several other less substantial revisions to the PI were agreed to in a series of discussions with the applicant, the committee determined that the prescribing information as it pertains to concomitant administration is acceptable.

7. Postmarketing

No safety signals were identified in the data submitted to the supplement. The applicant has not proposed, and the Agency will not require, any postmarketing studies with regard to concomitant administration.

8. Recommendation

The committee recommends approval of the BLA supplement for concomitant administration of Gardasil with Adacel and Menactra.