Summary Basis for Regulatory Action

Date: September 3, 2014

From: Lucia H. Lee, sBLA Committee Chairperson

Through: Wellington Sun, Director, DVRPA

BLA/ STN#: 125089/549

Applicant Name: Sanofi-Pasteur, Inc.

Date of Submission: November 6, 2013

PDUFA Goal Date: September 6, 2014

Proprietary Name/ Established Name: Menactra/ Meningococcal (Groups A, C, Y, W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (MenACWY-D)

Reason for the Submission: To revise the package insert to include safety and immunogenicity data to support Menactra revaccination at 15 years through 55 years of age in adolescents and adults at continued risk for meningococcal disease, if at least 4 years have elapsed since the prior dose.

Recommended Action: Approval

Signatory Authorities Action: Approval

Office Signatory Authority: Wellington Sun, Director, Division of Vaccines and Related Products Applications, 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.

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<th>Material Reviewed/ Consulted</th>
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<tr>
<td>Clinical Review</td>
<td>Anuja Rastogi, MD, MHS</td>
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<td>David C. Staten, Jr., MPH</td>
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1. Introduction
Menactra (MenACWY-D) is tetravalent meningococcal conjugate vaccine that contains serogroup A, C, Y, and W polysaccharide antigens, which are each conjugated to diphtheria toxoid protein. MenACWY-D was licensed in the US in 2005.

In this submission, the Applicant proposes to update the Menactra package insert with safety and immunogenicity data from study MTA-77 to support Menactra revaccination at 15 years through 55 years of age in adolescents and adults who previously received a single dose.

2. Background
At present, the CDC Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of adolescents with a tetravalent meningococcal conjugate (MCV4) vaccine at 11-12 years of age, with a booster dose at age 16 years. For adolescents vaccinated with MCV4 at 13-15 years of age, another dose is recommended at 16-18 years of age.

3. Chemistry Manufacturing and Controls (CMC)
The serum bactericidal activity (SBA) assay using human complement (HC), performed at Sanofi Pasteur by -------(b)(4)------------------, is adequate for its intended use.

There are no ongoing or impending investigations or compliance actions with respect to Sanofi-Pasteur’s facilities or products.

4. Nonclinical Pharmacology/Toxicology
No new pharmacology/toxicology data were submitted as part of this supplement.

5. Clinical Pharmacology
No new pharmacology data were submitted as part of this supplement.

6. Clinical/ Statistical
The safety and immunogenicity of MenACWY-D was evaluated in study MTA-77, an open-label, single group study that enrolled 834 individuals < 56 years of age who had received MenACWY-D 4-6 years previously at age ≥ 11 years. The primary objective was to evaluate SBA-HC responses to meningococcal serogroups A, C, Y, and W-135 induced by MenACWY-D in subjects in the population described above. Antibody kinetics of serogroup-specific SBA-HC responses was assessed in a subset of subjects. Subjects received 1 dose of MenACWY-D on Day 0. Blood specimens were obtained prior to and 28 days following vaccination. An additional blood sample was collected from 120 subjects 6 days (window: 5–7 days) post-vaccination. There were no major statistical issues.

Among the all-enrolled population, the mean age of subjects was 17.8 years (range: 15.0 to 53.7 years). The proportions of subjects with pre-vaccination SBA-HC antibody titers ≥ 1:8 were 64.5%, 44.2%, 38.7% and 68.5% for serogroup A, C, Y, and W, respectively. One month after vaccination, the proportions of subjects with SBA-HC titer ≥ 1:8 was 99.4%, 99.6%, 99.7% and 99.9% for serogroup A, C, Y, and W, respectively. The lower limit of the 1-sided 95% CI was 98.7% or higher for each serogroup, which met the pre-specified success criterion of 85%. At least 98.2% of subjects achieved titers ≥ 1:8 on Day 6 (98.2% for serogroup A and 99.1% for serogroups C, Y, and W-135); the data are consistent with an anamnestic response.
The most frequently solicited local reaction reported during the 7 day post-vaccination period was injection-site pain, which was experienced by 60.2% of subjects. The most common solicited systemic reactions were myalgia and headache reported by 42.8% and 38.6% of subjects, respectively. The majority of solicited reactions were characterized as mild or moderate, and lasted 1 to 3 days. Unsolicited AE assessed through Day 28 occurred in 29.5% of subjects. Most commonly reported were nasopharyngitis, headache, cough, and oropharyngeal pain. A total of 12 SAEs were reported by 11 subjects throughout the 6-month follow-up post-vaccination, which were considered by the study investigator and the CBER clinical reviewer to be unrelated to vaccination. The safety of MenACWY-D characterized in the study is acceptable.

This study was not conducted to fulfill Pediatric Research Equity Act (PREA) requirements.

7. Advisory Committee Meeting

There were no issues pertaining to this supplement that required input from the Vaccines and Related Biological Products Advisory Committee.

8. Labeling

Main changes to the package insert were as follows: Dosage and Administration (section 2): added “A single booster dose may be given to individuals 15 through 55 years of age at continued risk for meningococcal disease, if at least 4 years have elapsed since the prior dose”; Clinical Trial Experience (section 6.1): added description of study design and included safety data; Clinical Studies-immunogenicity (section 14.2): included immunogenicity results.

9. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

The Committee recommends approval of the Applicant’s supplemental BLA.

b) Risk/Benefit Assessment

The safety and immunogenicity data from this study support that the benefits of MenACWY-D immunization individuals who had received MenACWY-D 4-6 years previously at age ≥ 11 years outweigh the risks of developing adverse safety outcomes.

c) Recommendation for Postmarketing Risk Management Activities

No specific safety concerns were identified from the committee’s review of this study. No changes in postmarketing risk management activities are recommended.

d) Recommendation for Postmarketing Activities

No changes in the Applicant’s pharmacovigilance plan are recommended.