CMC Review Memorandum

Date: April 16, 2020

To: Biologics License Application Submission Tracking Number #125701/0

From: Xiao Wang, DVP, CMC Reviewer

Through: Haruhiko Murata, DVP

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Applicant: Sanofi Pasteur Inc.

Product: MenQuadfi – Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

STN: BLA STN 125701

Subject: Review of Serological Assay and Results for Human Papillomavirus Quadrivalent Vaccine Administered Concomitantly with MenQuadfi in Clinical Study MET50

Action Due Date: April 25, 2020

Materials Reviewed:

Original BLA:

- Section 2.5. Clinical Overview
  4.2.2.2 - Non-Inferiority of Concomitant Administration of MenACYW Conjugate Vaccine, Tdap, and HPV vaccine
- Section 2.7.3. Summary of Clinical Efficacy
  1.1.1.1.2 Background and Overview of Study MET50
  2.2 Summary of Results of Study MET50
- MET50 - Final Clinical Study Report
- MET50 - Appendix 1: Protocol and Protocol Amendment(s)

Cross-referenced Master File (b) (4):

- SOP BDTM-000029, HPV 6, 11, 16, and 18 Competitive Luminex Immunoassay, Version (b) (4) (HPV-4cLIA (b) (4))
- Partial Validation of the Human Papillomavirus 6, 11, 16, & 18 (b) (4) Competitive Luminex Immunoassay (HPV-4cLIA (b) (4)), Statistical Report 26-Oct-2016

Summary:

This memo describes the immunogenicity results of the HPV Quadrivalent vaccine, GARDASIL®, in the concomitant study MET50 submitted by Sanofi Pasteur in support of the BLA submission for a Meningococcal (Groups A, C, Y, W) polysaccharide tetanus toxoid conjugate vaccine, MenQuadfi (referred to below as MenACYW conjugate vaccine).

The HPV-4 cLIA (b) (4) (HPV 6, 11, 16 & 18, Competitive Luminex Immunoassay) is a serology assay used to measure immune responses to the HPV quadrivalent vaccine. The assay has been described and submitted to Master File BBMF (b) (4) by (b) (4) . In support of the current BLA application, a letter of authorization to allow cross-reference to BBMF (b) (4) was submitted to FDA by Sanofi Pasteur Inc.

From the HPV-associated immunogenicity results in the MET50 study, non-inferiority of HPV vaccine after the 3-dose series when the first dose was administered concomitantly with MenACYW conjugate vaccine and Tdap vaccine (Adacel®) compared with when the first dose of HPV vaccine was administered with Tdap vaccine alone was demonstrated based on the measured antibody titers, as well as the percentages of subjects who achieved HPV seroconversion for the particular immunized HPV types.

Recommendation: The HPV-4cLIA (b) (4) assay is suitable for its intended use. The non-inferiority of HPV vaccine administered concomitantly with Tdap or with Tdap and MenACYW was demonstrated in the concomitant MET50 study.

Background:

MenQuadfi:

MenQuadfi, a Meningococcal (Groups A, C, Y, W) Conjugate Vaccine, is indicated for active primary and booster immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y, and W. It is a sterile solution for intramuscular injection supplied in 0.5-mL single-dose vials. MenQuadfi is indicated for use in individuals 2 years of age and older.

Concomitant Study – MET50

MET50 was a Phase II, open-label, randomized, parallel-group, multi-center study to evaluate the immunogenicity and safety profiles of a single dose of MenACYW conjugate vaccine compared with that of the licensed vaccine, Menveo. The study also evaluated whether

MenACYW conjugate vaccine and the licensed vaccines for the adolescent age group, Adacel® (tetanus, diphtheria, acellular pertussis [Tdap] vaccine) and GARDASIL® (human papillomavirus [HPV] vaccine), exhibit any interference in terms of their immunogenicity when administered in healthy, meningococcal vaccine-naive adolescents 10 through 17 years of age.

A total of 1715 subjects were randomized to one of 4 groups to receive:
Group 1 - Single dose of MenACYW conjugate vaccine: 505 subjects
Group 2 - Single dose of Menveo: 507 subjects
Group 3 - Single dose of MenACYW conjugate vaccine, Tdap and HPV vaccines: 403 subjects
Group 4 - Tdap and HPV vaccines: 300 subjects

Subjects received vaccine(s) according to the schedule shown in Table 1 below. Subjects in all groups provided a pre-vaccination blood sample at Visit 1 (D0) and a post-vaccination sample at Visit 2 (23 to 37 days after the vaccination at Visit 1). Subjects in Group 3 and Group 4 provided an additional blood sample at D210 (Visit 5, 23 to 37 days after HPV vaccination at Visit 4).

Table 1: MET50 study groups and vaccination schedule

Group	D0, Visit 1	D60, Visit 3	D180, Visit 4
1	MenACYW conjugate vaccine	NA	NA
2	Menveo®	NA	NA
3	MenACYW conjugate vaccine Tdap, HPV	HPV	HPV
4	Tdap, HPV	HPV	HPV

GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) vaccine, Recombinant]

GARDASIL® (HPV) is a vaccine indicated in individuals 9 through 26 years of age for the prevention of diseases caused by HPV types 6, 11, 16, and 18. It is supplied as a 0.5-mL single-dose suspension for intramuscular injection at 0, 2 and 6 months. The vaccine was licensed to Merck & Co., Inc. in 2006.

HPV 6, 11, 16 & 18 (b) (4) Competitive Luminex Immunoassay (HPV-4 cLIA (b) (4))

HPV-4 cLIA (b) (4) is a serology assay used to measure antibodies to type-specific neutralizing epitopes on HPV virus-like particle (VLP) types 6, 11, 16, and 18. The assay, owned by (b) (4), has been developed to support clinical testing of the HPV quadrivalent vaccine. Documents for the description of the assay and assay validation protocols and statistical reports have been submitted to BBMF (b) (4). These documents were reviewed by Dr. Haruhiko Murata (the review memo is available in EDR system); HPV-4 cLIA (b) (4) was found to be suitable for its

intended purpose.

For the clinical study MET50, the HPV-4 cLIA (b) (4) assay for the anti-HPV antibody measurement was performed at (b) (4) in support of the current BLA application, a letter of authorization to allow cross-reference to BBMF (b) (4) was submitted to FDA by Sanofi Pasteur Inc.

Study MET50 - HPV-related Immunogenicity Results

One of the secondary immunogenicity objectives for the study MET50 was to evaluate the antibody responses to the antigens present in HPV vaccine after the 3-dose series, when the first dose of HPV vaccine is given concomitantly with MenACYW conjugate vaccine and Tdap vaccine (Group 3), compared with those when the first dose of HPV vaccine is given with Tdap vaccine only (Group 4).

Thirty days after receiving the 3rd dose of the HPV vaccine, the geometric mean titers (GMTs) of antibodies against the HPV antigens 6, 11, 16, and 18 in Group 3 were demonstrated to be non-inferior to the GMTs in Group 4 (Table 2). The lower limit of the 2-sided 95% CI of the ratio of the GMTs from the 2 groups was greater than 2/3 (0.667) for each antigen (Table 2).

Table 2: MET50 – secondary objective 3, comparison of the GMTs of HPV at D210 between Group 3 and Group 4

HPV Type	Group 3 MenACYW + Tdap + HPV (N=242) M	Group 3 MenACYW + Tdap + HPV (N=242) GMT3	Group 4 Tdap + HPV (N=164) M	Group 4 Tdap + HPV (N=164) GMT4	Group 3 / Group 4 GMT3 / GMT4 Ratio	Group 3 / Group 4 GMT3 / GMT4 2-sided 95% CI for ratio	Non-inferiority
6	242	800	164	800	1.00	(0.758; 1.320)	Yes
11	242	1492	164	1402	1.06	(0.861; 1.316)	Yes
16	242	6002	164	6395	0.939	(0.727; 1.212)	Yes
18	242	1271	164	1118	1.14	(0.886; 1.458)	Yes

Abbreviation: M, number of subjects with valid serology results for the particular HPV type

Thirty days after receiving the 3rd dose of the HPV vaccine, the percentages of subjects who achieved an HPV seroconversion for HPV types 6, 11, 16, and 18 in Group 3 were compared with the corresponding percentages of subjects in Group 4 (Table 3). The lower limit of the 2-sided 95% CI of the % differences between the two groups was greater than -10% (Table 3), thus demonstrating non-inferiority.

Table 3: MET50 – secondary objective 3, comparison of the proportions of subjects achieving HPV seroconversion at D210 between Group 3 and Group 4

HPV Type	Group 3 MenACYW + Tdap + HPV (N=242) n/M	Group 3 MenACYW + Tdap + HPV (N=242) P3 (%)	Group 3 MenACYW + Tdap + HPV (N=242) (95% CI)	Group 4 Tdap + HPV (N=164) n/M	Group 4 Tdap + HPV (N=164) P4 (%)	Group 4 Tdap + HPV (N=164) (95% CI)	Group 3- Group 4 P3 - P4 difference (%)	Group 3- Group 4 P3 - P4 2-sided 95% CI for difference	Non-inferiority
6	236/242	97.5	(94.7; 99.1)	157/164	95.7	(91.4; 98.3)	1.8	(-1.8; 6.3)	Yes
11	241/242	99.6	(97.7; 100.0)	162/164	98.8	(95.7; 99.9)	0.8	(-1.3; 3.9)	Yes
16	240/242	99.2	(97.0; 99.9)	162/164	98.8	(95.7; 99.9)	0.4	(-1.9; 3.6)	Yes
18	240/242	99.2	(97.0; 99.9)	162/164	98.8	(95.7; 99.9)	0.4	(-1.9; 3.6)	Yes

Reviewer's Comments and Conclusions:

- The validated HPV-4 cLIA (b) (4) serological assay was used for the assessment of immunogenicity endpoints to the HPV quadrivalent vaccine. The assay is suitable for the intended purpose in the clinical concomitant study MET50.

- On the basis of HPV-related immunogenicity results reported in study MET50, responses to HPV vaccine after the third dose were non-inferior when MenACYW conjugate vaccine was concomitantly administered together with HPV vaccine and Tdap vaccine as measured by GMTs and seroconversion rates for each of the HPV types (6, 11, 16, and 18).