Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

To:	Joseph Temenak, PhD Office of Vaccine Research and Review
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From:	Bethany Baer, MD Medical Officer, PVB, DE, OBE, CBER
Subject:	Review of the Pharmacovigilance Plan
Applicant:	Sanofi Pasteur
Product:	Meningococcal (Groups A, C, Y, W) Conjugate Vaccine (MenQuadfi)
Submission STN:	125701/0
Submission Date:	April 26, 2019
Action Due Date:	April 25, 2020

1 INTRODUCTION

A. Background

Meningococcal disease is a serious and sometimes fatal infection caused by *Neisseria meningitidis* bacteria. The annual incidence in the U.S. from 2006-2015 was 0.26 cases per 100,000 population. For the same time period, there was a case fatality rate of 14.9%.[1] In non-fatal cases, there can be long term complications including hearing loss, limb amputation, and other sequelae. Invasive disease is typically caused by 5 serogroups: A, B, C, Y, and W-135. There are currently two U.S.-licensed quadrivalent conjugate vaccines available for serogroups A, C, Y, and W-135 (Menactra and Menveo) and two vaccines for serogroup B (Bexsero and Trumenba). The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with a quadrivalent meningococcal conjugate vaccine for adolescents age 11-12 with a booster dose at age 16 years.[2]

B. Product Information

MenQuadfi is a quadrivalent meningococcal polysaccharide tetanus toxoid conjugate vaccine developed to protect against *N. meningitidis* serogroups A, C, Y, and W (also referred to as W-135). It is a liquid solution for intramuscular injection. The initial proposed age of use is for individuals 2 years of age and older. The proposed dose is a single 0.5-mL injection in patients who have not previously had a meningococcal vaccine. Individuals who have been primed with a meningococcal vaccine previously would receive a single booster dose of MenQuadfi.

C. Regulatory History

MenQuadfi has not been licensed in any country.

2 OBJECTIVE

This memorandum is in response to a request from the Office of Vaccine Research and Review (OVRR) to the Division of Epidemiology (DE) to review the Pharmacovigilance Plan for MenQuadfi.

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[1] MacNeil JR, Blain AE, Wang X, et al. Current Epidemiology and Trends in Meningococcal Disease – United States, 1996-2015. Clin Infect Dis. 2018 Apr 2;66(8): 1276-1281.

[2] Centers for Disease Control and Prevention. Updated Recommendations for Use of Meningococcal Conjugate Vaccines - Advisory Committee on Immunization Practices (ACIP), 2010. MMWR. 2011;60(03):72-76.

3 MATERIALS REVIEWED

Source	Subtype	Document Reviewed
Sanofi Pasteur	125701/0	Integrated Summary of Safety, V. 2, Aug. 22, 2018
Sanofi Pasteur	125701/0	Summary of Clinical Safety
Sanofi Pasteur	125701/0	Risk Management Plan, V. 1, Dec. 15, 2018
Sanofi Pasteur	125701/0.5	BLA amendment, Four Month Safety Update, dated Aug. 16, 2019
Sanofi Pasteur	125701/0.10	BLA amendment, Efficacy Information Request Response, submitted Oct. 14, 2019
Sanofi Pasteur	125701/0.28	BLA Amendment, Response regarding FDA labeling comments, submitted Mar. 13, 2020.
Sanofi Pasteur	125701/0.34	BLA amendment, Response to Mar. 26, 2020 request regarding labeling, submitted Apr. 3, 2020
Sanofi Pasteur	125701/0.35	BLA amendment, Response to Mar. 12, 2020 request regarding title and milestone dates for the pregnancy registry PMC, submitted Apr. 3, 2020
Published literature	Various	See footnotes

4 CLINICAL SAFETY DATABASE[3]

A. Integrated Safety Dataset

At the time of the analysis of the integrated safety dataset, there were 8 completed clinical trials for MenQuadfi. Two of the clinical trials used an earlier formulation of the vaccine and focused on infants and toddlers, so they are not included in the integrated safety dataset. The remaining 6 clinical trials in children, adolescents, and adults comprise the safety dataset and are summarized in the table below. There were 5,118 subjects who received a single dose of the final formulation of MenQuadfi during these 6 studies. All 6 of the studies were conducted in the U.S., with two of the studies also including subjects in Puerto Rico. Five of the studies included adverse event (AE) follow-up to 6 months post-vaccination, while the sixth study (MET44) had follow-up to approximately 6 weeks post-vaccination. All of the safety analyses for the integrated safety dataset were descriptive. The summary of results focuses on the percentage of subjects who received MenQuadfi and had an adverse event. The different studies had different comparator vaccines (e.g. Menactra, Menveo, or Menomune) so there is not a single comparator percentage calculated for AEs in the integrated safety dataset.

[3] Information from Integrated Safety Summary and Summary of Clinical Safety for BLA 125701/0.

Table 1: Studies comprising the MenQuadfi Integrated Safety Dataset[4]

Study Phase	Description	Age	Test Products & Sample Size
MET35 Phase III	Safety & Immunogenicity Non-Inferiority v. Menveo	2 through 9 years old	MenQuadfi - 499 Menveo - 501
MET43 Phase III	Safety, Immunogenicity, Lot Consistency and Non-Inferiority v. Menactra	10 through 55 years old	MenQuadfi Lot 1 – 902 MenQuadfi Lot 2 – 895 MenQuadfi Lot 3 – 906 Menactra - 641
MET44 Phase II	Safety & Descriptive Immunogenicity v. Menomune	≥56 years old	MenQuadfi – 201 Menomune - 100
MET49 Phase III	Safety & Immunogenicity Non-Inferiority v. Menomune	≥56 years old	MenQuadfi – 451 Menomune – 455
MET50 Phase II	Safety, Immunogenicity Non-Inferiority v. Menveo, and v. Concomitant Use with Tdap and HPV	10 through 17 years old	MenQuadfi – 505 Menveo – 507 MenQuadfi, Tdap, HPV-403 Tdap and HPV - 300
MET56 Phase III	Safety, Immunogenicity Non-Inferiority v. Menactra in MCV4 Primed Subjects	≥15 years old	MenQuadfi – 403 Menactra - 407

The studies of the integrated safety dataset evaluated immediate unsolicited adverse events (AEs) (0-30 minutes after vaccination), pre-defined solicited injection site or systemic reactions (within 7 days after vaccination), unsolicited non-serious AEs (within 30 days after vaccination), medically attended adverse events (MAAEs) (until end of study for all except for MET44), serious adverse events (SAEs) (related and unrelated, until end of study for all except MET44), deaths (throughout the study), and AEs leading to discontinuation (throughout the study).

The demographics and baseline characteristics for subjects included in the integrated safety dataset were comparable between MenQuadfi and the control groups within each age study.

B. Adverse Events from the Clinical Trials

The most commonly reported solicited injection site reaction was pain, which occurred in 38.3% of the MenQuadfi group. Erythema and swelling were also

[4] Table compiled from Integrated Safety Summary, p. 8-9 and Summary of Clinical Safety, p. 159-164.

reported but were less frequent. The most commonly reported solicited systemic reactions in the MenQuadfi group were myalgia (30.7%) and headache (26.4%).

The percentage of MenQuadfi subjects with at least 1 unsolicited adverse reaction (AR) within 30 days of vaccination was 2.8%. The most common systemic ARs were dizziness (0.3%), fatigue (0.2%), and nausea (0.2%).

The percentage of MenQuadfi subjects with 1 or more medically attended adverse events (MAAEs) in the 30 days after vaccination was 6.5%. This is compared to 6.0% for Menactra and 12.0% for Menveo. For Day 31 to the end of the 6-month follow-up period, the percentage of MAAEs for MenQuadfi was 15.7%. This percentage was lower than the percentage seen for Menactra (17.3%) and for Menveo (27.6%). The majority of the MenQuadfi MAAEs were in the system, organ, class (SOC) category of "Infections and Infestations." The sponsor reports that there were no safety concerns arising from the review of the MAAEs.

There were no deaths reported in the MenQuadfi group during the study. There were two deaths in patients in the Menomune group. One death was due to metastatic lung cancer, and the other death was spinal dislocation due to a road traffic accident. There were no MenQuadfi subjects who withdrew from the study due to an SAE.

The percentage of MenQuadfi subjects who had at least 1 SAE in the first 30 days after vaccination was 0.3%. "Nervous System Disorders" was the most common SOC for this group. For Day 31 to the end of the 6-month study period, the percentage of MenQuadfi subjects with one or more SAEs was 1.0%. The majority of the SAEs between day 31 and the end of the study were from the Infections and Infestations SOC. None of the SAEs were considered related to MenQuadfi.

A single study, MET35, specifically collected information on the following adverse events of special interest: Kawasaki disease, Guillain-Barré syndrome, generalized seizures (including febrile seizures), and idiopathic thrombocytopenic purpura. There were no cases of these adverse events of special interest seen in the study.

Analyses of AEs by age group were also conducted for the integrated safety data. In children 2 through 9 years of age, MenQuadfi was compared with Menveo, and the safety profile was similar. MenQuadfi tended to have a lower injection site reactogenicity than Menveo in the 2- through 9-year-old children. For adolescents and adults who had previously received Menactra or Menveo, there was an increased frequency of injection site erythema and swelling but no increased severity or duration of the reaction. The remaining safety profile of MenQuadfi for the adolescent and adult age group was comparable to that of Menactra or Menveo. For older adults and the elderly, the rates of solicited

reactions, especially injection site reactions, were higher with MenQuadfi than with Menomune. This is likely due to the tetanus toxoid protein in MenQuadfi as Menomune does not contain any conjugate protein.

The clinical trials involving concomitant vaccines found that the safety profiles of Tdap and HPV vaccines were comparable when administered with or without MenQuadfi in adolescents. A study of MenQuadfi given as a booster dose in patients who had previously received Menactra or Menveo did not identify any safety concerns.

The sponsor concluded that in the clinical trials MenQuadfi was found to be well tolerated in different age groups and had a safety profile comparable to the other U.S.-licensed meningococcal vaccines. The four-month safety update submitted to the BLA stated that there was no new important information received for the proposed indication of 2 years of age and above.

C. Use During Pregnancy

The clinical trials excluded pregnant subjects, but there were 12 subjects who became pregnant during the studies. Seven of these received MenQuadfi outside of the window to be considered exposed during pregnancy (i.e., greater than 30 days prior to the last menstrual period [LMP]). Four were exposed between 30 days prior to the LMP and 7 days after the LMP and were considered exposed but not yet pregnant. One subject received MenQuadfi during pregnancy (7 days after the LMP to throughout the pregnancy). This single case of exposure during pregnancy was in a 20-year-old female who received MenQuadfi 36 days after her LMP. A healthy male was born without complication and without any congenital abnormalities at 41 weeks gestation.

5 POSTMARKETING DATA

There is no postmarketing data available for MenQuadfi as it has not been licensed in any country.

There is a different quadrivalent meningococcal conjugate vaccine for serogroups A, C, Y, W-135 with the tetanus toxoid carrier protein named Nimenrix. It is manufactured by Pfizer and is approved in the European Union and 43 additional countries but not in the U.S. Publications describing the Nimenrix clinical trials state that it has a safety profile similar to other licensed quadrivalent meningococcal conjugate vaccines.[5,6]

[5] Serra LD, York LJ, Balmer P, Webber C. Meningococcal Group A, C, W, and Y Tetanus Toxoid Conjugate Vaccine: A Review of Clinical Data in Adolescents. J Adolesc Health. 2018 Sep;63(3); 269-279.

[6] Dhillon S, Pace D. Meningococcal Quadrivalent Tetanus Toxoid Conjugate Vaccine (MenACWY-TT; Nimenrix): A Review. Drugs. 2017 Nov;77(17):1881-1896.

6 PHARMACOVIGILANCE PLAN

The Risk Management Plan (RMP) for MenQuadfi is version 1, dated Dec. 15, 2018. The sponsor notes that there were no unanticipated safety findings or important risks identified during the MenQuadfi clinical trials. Based on the safety profile of similar quadrivalent meningococcal vaccines licensed in the U.S., the important potential risks are: anaphylaxis, Guillain-Barré syndrome (GBS), and Bell's palsy. There were no cases of any of these three risks in the completed MenQuadfi clinical trials, except for one case of Bell's palsy classified by the investigator as unrelated to the vaccine. There have been cases of all three risks following the other U.S.-licensed meningococcal vaccines. The sponsor plans to follow these potential risks with routine pharmacovigilance and review of any related events in the Periodic Benefit-Risk Evaluation Reports (PBRERs). The sponsor will also follow-up each report of these three safety concerns with a targeted questionnaire.

Table 2: Applicant's Pharmacovigilance Plan for Important Risks

Type of Risk	Safety Concern	Planned Pharmacovigilance Activity
Identified	None	Not applicable
Potential	Anaphylaxis	Routine pharmacovigilance Targeted follow-up questionnaire
Potential	Guillain-Barré Syndrome	Routine pharmacovigilance Targeted follow-up questionnaire
Potential	Bell's Palsy	Routine pharmacovigilance Targeted follow-up questionnaire

A. Important Potential Risks

i. Anaphylaxis

Anaphylaxis, a severe hypersensitivity reaction, can be seen after any vaccine. It has been reported rarely after Menveo and Menactra. There were no cases of anaphylaxis in the MenQuadfi clinical trials.

ii. Guillain-Barré Syndrome

This potential risk arose because GBS has been associated with certain prior influenza vaccines (e.g., the 1976 swine flu vaccine) and was reported after Menactra. A postmarketing retrospective study of Menactra included 12.6 million 11- to 21-year-olds and found no confirmed cases of GBS occurring in the 6-week risk window following Menactra vaccination. The authors of the publication concluded that the upper 95% CI for the attributable risk of GBS associated with Menactra was estimated as 1.5 cases per 1 million doses.[7] The FDA evaluated

[7] Velentgas P, Amato AA, Bohn RL, et al. Risk of Guillain-Barré syndrome after meningococcal conjugate vaccination. *Pharmacoepidemiol Drug Saf*. 2012 Dec;21(12):1350-8. doi: 10.1002/pds.3321.

the study results and found that taking into account missing data, the attributable risk of GBS from Menactra ranged from 0 to 5 additional cases per 1 million vaccinees within the 6-week period following vaccination.

A VAERS search for the other U.S.-licensed meningococcal conjugate vaccines shows intermittent reports for GBS, and related terms including demyelinating polyneuropathy and nerve conduction studies abnormal, following vaccination.

An Institute of Medicine review in 1994 found evidence of a causal relationship between tetanus toxoid vaccines and GBS. An updated review by the same organization in 2011 stated that the evidence was inadequate to accept or reject a causal relationship.[8]

There were no cases of GBS during the MenQuadfi clinical trials. GBS is included in the Warnings and Precautions section of the MenQuadfi label.

iii. Bell's palsy

Bell's palsy and facial paresis have been reported after Menveo and Menactra. A PMC study of almost 50,000 patients found an imbalance of serious cases of facial paresis, specifically Bell's palsy, after Menveo. There were no cases of Bell's palsy classified by the investigator as related to MenQuadfi in the clinical trials. There was a case of Bell's palsy in Study MET43 that was non-serious and assessed by the investigator as not related to MenQuadfi. This case occurred in a 35-year-old woman at 135 days following MenQuadfi vaccination.[9]

B. Areas of Missing Information

Table 3 lists the areas of missing information for MenQuadfi and the associated planned pharmacovigilance activities. Table 4 lists the studies included in the pharmacovigilance plan.

Table 3: Applicant's Pharmacovigilance Plan for Areas of Missing Information

Area of Missing Information	Planned pharmacovigilance activity
Use during pregnancy and lactation	• Routine pharmacovigilance • Pregnancy registry (MEQ00070)
Use in immunocompromised and immunodeficient individuals	• Routine pharmacovigilance

[8] Stratton K, Ford A, Rusch E, et al., editors. Adverse Effects of Vaccines: Evidence and Causality. Washington (DC): The National Academies Press; 2012. P. 557-8.
[9] Efficacy Information Amendment 125701/0.10.

Area of Missing Information	Planned pharmacovigilance activity
Long term persistence of the immune response, and safety and immunogenicity of booster in individuals primed with MenQuadfi	• Routine pharmacovigilance • Targeted follow-up questionnaires for invasive meningococcal disease • Studies MET62, MET59, MEQ00066
Co-administration with MenB vaccine in adolescents	• Study MET59
Safety and immunogenicity in infants and toddlers less than 2 years of age	• Studies MET54, MET51, MET57, MEQ00065 in toddlers • Studies MET41, MET42, MET 61, MET52, MET58, MET33 in infants

Table 4: Studies included in the Pharmacovigilance Plan

Study Number and Study Description	Design	Safety follow-up	Status
MET33 Safety and Immunogenicity of a 3-Dose Schedule of MenQuadfi when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers	Phase III, open-label, randomized, parallel-group, active-controlled, multicenter study in Mexico and The Russian Federation, 525 subjects	30 days after the last vaccination	Study ongoing; Final study report planned in Q2 2022
MET41 Safety of MenQuadfi Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers	Phase III, modified double-blind, randomized, parallel-group, active controlled, multicenter study in the U.S., 3080 subjects	6 months after the last vaccination	Study ongoing; Final study report planned in Q3 2022
MET42 Immunogenicity and Safety of MenQuadfi when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers	Phase III, partially modified double-blind, randomized, parallel-group, active controlled, multi-center study in the U.S., 2475 subjects	6 months after the last vaccination	Study ongoing; Final study report planned in Q3 2023

Study Number and Study Description	Design	Safety follow-up	Status
MET51 Immunogenicity and Safety of MenQuadfi in Toddlers 12 to 23 Months of Age	Phase III, modified, double-blind, randomized, parallel-group, active-controlled, multicenter study in Germany, Spain, and Hungary, 914 subjects	30 days after vaccination	Study completed; Final study report completed in Dec. 2018
MET52 Immunogenicity and Safety of MenQuadfi in Infants and Toddlers when Administered Using a 1+1 Schedule in a National Schedule with MenB Vaccine	Phase III, open-label, randomized, parallel-group, active-controlled, multi-center study in the U.K., 700 subjects	30 days after the last vaccination	Study ongoing; Final study report planned in Q4 2022
MET54 Immunogenicity and Safety of MenQuadfi in Healthy Toddlers	Phase II, open-label, randomized, parallel active-controlled, multi-center study in Finland, 188 subjects	30 days after vaccination	Study complete; Final study report completed in June 2016
MET57 Immunogenicity and Safety of MenQuadfi Administered Concomitantly with Other Pediatric Vaccines in Healthy Toddlers	Phase III, open-label, randomized, parallel-group, active-controlled, multicenter study in South Korea, Thailand, Mexico and The Russian Federation, 1200 subjects planned	30 days after vaccination	Study ongoing; Final study report planned in Q2 2019
MET58 Immunogenicity and Safety of MenQuadfi when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Infants and Toddlers in Europe	Phase III, partially modified double-blind, randomized, parallel-group, active-controlled, multicenter study in Czech Republic, Finland, Romania, Sweden, Italy, and Spain, 1540 subjects	30 days after the last vaccination	Study ongoing; Final study report planned in Q2 2023

Study Number and Study Description	Design	Safety follow-up	Status
MET59 Immunogenicity and Safety of a Booster Dose of MenQuadfi in Adolescents and Adults	Phase IIIb, randomized, modified double-blind, parallel-group, active-controlled, multi-center clinical study in the U.S. and Puerto Rico, 400 subjects planned	6 months after vaccination	Study planned; Final study report planned in Q4 2021
MET61 Immunogenicity and Safety Study of MenQuadfi Administered in Healthy Infants and Toddlers	Phase III, randomized, parallel group, active-controlled, multi-center study in the U.S., 940 subjects	6 months after vaccination	Study ongoing; Final study report planned in Q3 2022
MET62 Immunogenicity and Safety of MenQuadfi as a Booster Dose in Children Vaccinated 3 Years Earlier as Toddlers	Phase III, open-label, multicenter clinical study in Finland, 188 subjects planned	30 days after vaccination	Study ongoing; Final study report planned in Q1 2020
MEQ00065 Immunogenicity and Safety of MenQuadfi v. Nimenrix or Neisvac-C in Healthy Toddlers 12-23 months of age	Phase III, modified double-blind, randomized, active-controlled, multicenter study in Germany, Finland, and Denmark, 673 subjects planned	30 days after vaccination	Study planned; Final study report planned in Q4 2020
MEQ00066 Safety and Immunogenicity of a Single Dose of MenQuadfi at least 3 Years Following Initial Vaccination with Either Menomune or MenQuadfi in Older Adults	Phase IIIb, randomized, open-label, multicenter clinical study in the U.S., 440 subjects planned	30 days after vaccination	Study planned; Initial study report planned in Q2 2020, Final study report addendum planned in Q3 2022

Study Number and Study Description	Design	Safety follow-up	Status
MEQ00070 Pregnancy Registry	Observational registry, 5 years of enrollment	9-month follow-up for pregnancy outcomes and 12-month follow-up for infant outcomes	Study planned; Planned protocol submission Nov. 2020; Final study report planned for July 2029

i. Use during Pregnancy and Lactation

A non-clinical study for developmental toxicity in rabbits found no indication of maternal systemic toxicity during gestation or lactation and no indication of teratogenicity with MenQuadfi exposure. As described in section 4C above, there was one inadvertent case of MenQuadfi exposure during pregnancy. There were no complications seen with the pregnancy, and a healthy full-term infant was born. There were four cases of women exposed in the 7-44 days prior to conception, and those pregnancies also resulted in live births without congenital abnormalities. The sponsor is planning a Pregnancy Registry (MEQ00070) to monitor, evaluate, and assess pregnancy and teratogenic effects in the offspring of women exposed to MenQuadfi before or during pregnancy. The title of the study is "The MenQuadfi Pregnancy Registry: A surveillance Registry to assess the safety of MenQuadfi among Exposed Pregnant Women and their offspring." There will be a 5-year enrollment period with a 9-month follow-up for pregnancy outcomes and a 12-month follow-up for infant outcomes. The registry is to start after product launch in 2020. The final protocol will be submitted by Nov. 30, 2020. There will be updates in the PBRERs. The study completion date is June 30, 2028, and a final study report is planned for June 30, 2029. At that point, a decision to close the registry or extend it will be made in agreement with the regulatory authorities.

ii. Use in immunocompromised and immunodeficient individuals

Immunocompromised patients were excluded from the clinical trials so the safety profile of this group is unknown. In addition to more common immunocompromising diseases, the RMP specifically states that this immunocompromised group includes persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation. The draft MenQuadfi label includes a section on altered immunocompetence in the Warnings and Precautions. Similar to the label changes made for the other meningococcal vaccines, this section states that persons with complement deficiencies or receiving treatment that inhibits terminal complement activation (e.g., eculizumab) are at increased risk for invasive

meningococcal disease, even if they develop antibodies following MenQuadfi vaccination. This safety risk will be monitored with routine pharmacovigilance.

iii. Long term persistence of the immune response, and safety and immunogenicity of booster in individuals primed with MenQuadfi

In addition to routine pharmacovigilance, the sponsor will use targeted questionnaires to follow-up on reports of invasive meningococcal disease. The planned clinical studies MET62, MET59, and MEQ00066 will provide more information on the long-term immune response and safety of a booster dose of MenQuadfi.

iv. Co-administration with MenB vaccine in adolescents

Quadrivalent meningococcal conjugate vaccines are often given concomitantly with meningococcal B vaccines at the 16-year well child visit. MenQuadfi study MET59 will assess concomitant administration with meningococcal B vaccines.

v. Safety and immunogenicity in infants and toddlers less than 2 years of age

The currently proposed age of use with the application is 2 years of age and above. The sponsor is conducting additional clinical studies in toddlers (MET54, MET51, MET57, MEQ00065) and in infants (MET41, MET42, MET61, MET33, MET52, MET58, MET61).

7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

The sponsor's pharmacovigilance plan includes the important potential risks of anaphylaxis, GBS, and Bell's palsy, all of which have been reported with other meningococcal vaccines. The other U.S.-licensed meningococcal conjugate vaccines also include the following potential risks for one or both products: thrombocytopenia, acute disseminated encephalomyelitis, vasculitis including Kawasaki disease, vaccination failure, febrile seizure, and new onset autoimmune diseases. These additional potential risks were included for Menveo or Menactra based on pre-licensure trial cases or post-licensure reports with those vaccines. The MenQuadfi study MET35 specifically looked for events of Kawasaki disease, GBS, seizures, idiopathic thrombocytopenic purpura and did not find any cases. Menactra's pharmacovigilance plan lists anaphylactic reaction and vasovagal syncope as identified risks. MenQuadfi lists anaphylaxis as a potential risk and includes syncope in the Warnings and Precautions section of the package insert. Menveo has the identified risk of reconstitution errors which is specific to its two-vial presentation but is not relevant for MenQuadfi. Regarding the planned pregnancy registry for MenQuadfi, the other two quadrivalent meningococcal conjugate vaccines have each had pregnancy registries. Menveo completed a pregnancy registry with three years of enrollment, and Menactra's pregnancy registry is ongoing with over 10 years of enrollment. Taking these different considerations into account, MenQuadfi's pharmacovigilance plan is adequate for the safety profile.

8 OBE/DE RECOMMENDATIONS

- The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety postmarketing requirement (PMR) study at this time.
- DE agrees with the pharmacovigilance activities proposed by the applicant in the Risk Management Plan along with adverse event reporting as required under 21CFR600.80.
- OBE/DE supports the sponsor's plan to establish a pregnancy registry as a Postmarket Commitment entitled "The MenQuadfi Pregnancy Registry: A Surveillance Registry to assess the safety of MenQuadfi among Exposed Pregnant Women and their offspring." The milestone dates are:
    - Final Protocol Submission: Nov. 30, 2020
    - Study Completion Date: June 30, 2028
    - Final Report Submission: June 30, 2029