Summary Basis of Regulatory Action

Date: September 16, 2016

From: LCDR Theodore Garnett, Ph.D., Chair of the Review Committee

BLA/STN: 125089/593

Applicant Name: Sanofi Pasteur Limited

Date of Submission: November 17, 2016

PDUFA Goal Date: September 16, 2016

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

Indication: Menactra is indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135. Menactra is approved for use in individuals 9 months through 55 years of age. Menactra does not prevent *N meningitidis* serogroup B disease.

This supplement was submitted to include immunogenicity and safety data from Study MTA43 to support the co-administration of Menactra with a fifth dose of Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DAPTACEL) in children 4 through 6 years of age.

Recommended Action: Approval

Signatory Authority's Action: Approval

Office's Signatory Authority: Wellington Sun, M.D., Director, DVRPA

☒ **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 – Document Date
Clinical Review	Anuja Rastogi, M.D. – September 15, 2016
Statistical Review (Clinical)	Zhong Gao, Ph.D. – August 15, 2016
Product Review (aP, D & T Serology Assays)	Freyja Williams, B.S. – February 5, 2016
Product Review (Poliovirus Serology Assays)	Majid Laassri, Ph. D. – June 14, 2016
Bioresearch Monitoring Review	Bhanumahti Kannan, M.S. – July 20, 2016
Pharmacovigilance Review	Bethany Baer, M.D. – September 13, 2016
Labeling Review	Theodore Garnett, Ph.D. – September 16, 2016

1. INTRODUCTION

On October 27, 2015, Sanofi Pasteur Inc. submitted Prior Approval Supplements to the BLAs for Menactra® and DAPTACEL® with proposed labeling changes resulting from a concomitant administration study (Study MTA43) of Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Menactra) and a fifth dose of Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DAPTACEL) in children 4 to 6 years of age in the US. Following discussions between the Agency and the Applicant, these submissions were reclassified as efficacy supplements on November 17, 2015, to accommodate the review of the clinical data contained in the Final Clinical Study Report for Study MTA43. The clinical data in Study MTA43 was submitted with the Menactra efficacy supplement and by cross reference via a Letter of Authorization included in the DAPTACEL efficacy supplement.

Study MTA43 evaluated immunogenicity and safety of the co-administration of Menactra and DAPTACEL in children 4 years through 6 years of age at either the same visit or sequentially 30 days apart. Data from this study was used to update the Package Inserts (PIs) of both Menactra and DAPTACEL. The Applicant's proposed labeling changes included the addition of data to Section 6 (Adverse Reactions), Section 14 (Clinical Studies), and Section 5 (Warning and Precautions), and language on the preferred sequence in which Menactra and DAPTACEL should be administered. Upon CBER's request, the Applicant also proposed changes to Section 8 to satisfy new regulatory requirements regarding the Pregnancy and Lactation Labeling Rule (PLLR).

The most significant finding from this study was the reduced meningococcal hSBA responses to all vaccine serogroups when Menactra was administered 30 days after DAPTACEL. These findings are important as only those individuals at increased risk for meningococcal disease are recommended to receive meningococcal quadrivalent vaccination. If quadrivalent meningococcal conjugate vaccination with Menactra is required prior to school entry, then the timing of vaccination with Menactra and DAPTACEL would need to be considered by the health care provider in order to prevent sub-optimal immune response to Menactra vaccination.

2. BACKGROUND

Menactra is a tetravalent vaccine composed of 4 meningococcal capsular polysaccharides (groups A, C, Y, and W-135) that have been individually conjugated to Diphtheria Toxoid and is indicated for the prevention of disease caused by *N. meningitidis*. Menactra was licensed for use and distribution in the US in 2005 for individuals 11 through 55 years of age. In 2007 the age range for use was extended to include persons 2 through 10 years of age, and in 2011 approved for use in children 9 through 23 months of age. Each 0.5 mL dose of the vaccine contains 4 micrograms each of the 4 polysaccharides conjugated to approximately 48 mcg of diphtheria toxoid protein carrier. Children 9 through 23 months of age are given a 2-dose series at least 3 months apart while individuals 2 through 55 years of age are given a single dose.

DAPTACEL (also referred to as DTaP in this document) is a combination vaccine which contains adsorbed diphtheria and tetanus toxoids and the following pertussis antigens: pertussis toxoid (PT), filamentous hemagglutinin (FHA), and fimbriae types 2 and 3 (FIM), and pertactin (PRN). Each 0.5 mL dose of the vaccine contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid

and acellular pertussis antigens [10 mcg PT, 5 mcg FHA, 3 mcg PRN, and 5 mcg FIM]. DAPTACEL was licensed in the US in 2002 for use in infants and children aged 6 weeks through 6 years of age (prior to 7th birthday) as a 5-dose series administered at 2 months, 4 months, 6 months, 15-18 months and 4-6 years of age to protect against diseases caused by *Bordetella pertussis*, *Clostridium tetani*, and *Corynebacterium diphtheriae.*

The US Advisory Committee on Immunization Practices (ACIP) currently recommends the routine administration of a 5th dose of a DTaP containing vaccine, such as DAPTACEL, in children 4 to 6 years of age at the time of school entry. Vaccination with a meningococcal quadrivalent conjugate vaccine, such as Menactra, is only recommended for use in children 4 through 6 years of age if they are at high risk for meningococcal disease due to an underlying condition or if they are at increased risk due to travel. The Applicant's rationale for conducting Study MTA43 was to assess the safety and immunogenicity of co-administration of Menactra with DAPTACEL at the time of school entry.

3. CHEMISTRY MANUFACTURING and CONTROL (CMC) AND CLINICAL SEROLOGICAL ASSAY INFORMATION

The Menactra and DAPTACEL clinical lots used in Study MTA43 were manufactured as described in the respective biologic license applications (BLAs) for these products. No changes to the approved manufacturing processes were submitted in the application.

Validation reports and additional data were reviewed for serological assays used in Study MTA43 to quantitate antibody responses to meningococcal polysaccharides (groups A, C, W-135 and Y); diphtheria, tetanus and pertussis antigens (PT, FHA, PRN, FIM); and poliovirus Types 1, 2, and 3.

Serological Assays for Meningococcal Polysaccharides, Diphtheria, Tetanus and Pertussis Antigens

The assays used to measure antibodies against the diphtheria, tetanus, pertussis and meningococcal polysaccharides appeared to perform adequately for use in study MTA43. These assays included serum bacterial assays using human complement (hSBA) for meningococcal antigens, the [redacted] for diphtheria, and the ELISA method for tetanus and pertussis antigens. Review of the clinical serology data and assay validation reports did not indicate any issues related to assay performance and the assays are suitable for the intended use in this supplement.

Serological Assay for Poliovirus Types 1, 2, and 3

Although Study MTA43 evaluated immunogenicity data generated from co- administration of Menactra and DAPTACEL, study subjects also received Poliovirus Inactivated (IPOL®) according to immunization recommendations to maintain the blind. Antibody titers against poliovirus Types 1, 2, and 3 were measured as observational immunogenicity endpoints by the poliovirus [redacted] thirty days after IPOL vaccine administration. The assay validation reports demonstrated that all performance benchmarks were met and no major changes were reported to materials, equipment or procedures. The assay is validated and is suitable for the intended use in the supplement.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No new non-clinical data was submitted in this application.

5. CLINICAL PHARMACOLOGY/PHARMACOVIGILANCE

This supplemental BLA did not include new pharmacology/toxicology information.

6. CLINICAL/ STATISTICAL

Study MTA43 was a Phase 2, randomized, modified double-blind, 3-arm, parallel-group, comparative, multi-center study enrolling approximately 880 healthy US children 4 years through 6 years of age. The study participants were randomized to one of three study groups as described in the table below. All subjects received three study vaccines, Menactra, DAPTACEL, and IPOL over two study visits separated by 30 days. Each group was administered 2 study vaccines at Visit 1, and the 3rd study vaccine alone at Visit 2, as follows:

Table 1: MTA43 Study Groups

	Group A N:353	**Group B N: 353**	**Group C N=175**
Visit 1 (Day 0)	Daptacel + IPOL	Daptacel + Menactra	IPOL + Menactra
Visit 2 (Day 30)	Menactra	IPOL	Daptacel

The immune response generated to each vaccine component was assessed 30 days after the respective vaccination in each study group. The primary immunogenicity objective was to determine whether immune responses generated to the tetanus, diphtheria, and meningococcal vaccine components when Menactra and DAPTACEL were co-administered at the same visit are non-inferior to those observed when each vaccine is administered with IPOL. The secondary immunogenicity objectives were to determine whether the immune response to each pertussis antigen when the two vaccines were co-administered at the same visit, and the hSBA GMT responses when Menactra was administered one month after DAPTACEL were non-inferior to those observed when Menactra was administered one month before DAPTACEL. The evaluation of safety was descriptive and included 7 day post-vaccination assessment of solicited local and systemic reactions, 30 days post-vaccination assessment of unsolicited AEs, and monitoring of serious adverse events throughout the study duration.

The study endpoints were non-inferiority comparisons with pre-specified margins. The specific primary and secondary immunogenicity endpoints are as follows:

Primary Immunogenicity Endpoints:

- Percentage of subjects with antibody titers against diphtheria (measured by neutralization assay) and tetanus (measured by ELISA**) ≥ 1.0 IU/mL** 30 days after Daptacel vaccination in Group A (Visit 1: Daptacel + IPV) and Group B (Visit 1: Daptacel + Menactra)
  - *Study Success Criteria:* If the upper limit of the 2-sided 95% CI of (p_A - p_B) was < ***0.05***, non-inferiority was concluded.

- Geometric mean antibody titers (GMTs) against meningococcal serogroups A, C, Y, and W-135 (measured by hSBA) 30 days after Menactra vaccination in Group C (Visit 1: Menactra + IPV) and Group B subset (Visit 1: Menactra + Daptacel)
  - *Study Success Criteria:* If the upper limit of the 2-sided 95% CI of the GMT ratio (GMTC/GMTB) computed separately for each of the serogroups was **< *2***, non-inferiority was concluded.

Secondary Immunogenicity Endpoints:

- Geometric mean antibody concentrations (GMCs) against the pertussis antigens (PT, FHA, FIM, and PRN) (measured by ELISA) 30 days after Daptacel vaccination in Group A (Visit 1: Daptacel + IPV) and Group B (Visit 1: Daptacel + Menactra)
  - *Study Success Criteria*: If the upper limit of the 2- sided 95% CI of the adjusted GMC ratio (GMCA/GMCB) for each of the antigens was **< *1.5***, non-inferiority was concluded.

The study objectives evaluating the seroresponse rates to the diphtheria toxin (% participants with antibody concentrations > 1.0 IU/mL) and tetanus toxin (% participants with antibody concentrations > 1.0 IU/mL), in addition to the immune responses to PT, FHA, and PRN pertussis (GMCs) antigenic components of DAPTACEL when co-administered with Menactra at the same visit were met, but the non-inferiority criteria for the evaluation of FIM pertussis antigen was missed by a small margin (Tables 2 and 3).

Table 2: Percentage of Subjects with Antitoxin Concentrations against Diphtheria & Tetanus ≥1.0 IU/mL 30 days After Concomitant Administration of Daptacel+Menactra (Study Group B) vs. Daptacel +IPV (Study Group A), by Group – PPP

	Group A (N=250) **% [95%CI]**	**Group B (N=238)** **% [95%CI]**	**Upper Limit of 2-sided 95% CI for Difference in % (Group A-Group B)**
Subjects with diphtheria antitoxin concentration ≥ 1.0 IU/mL	99.6% [97.8,100.0]	100% [98.5,100.0]	0.4
Subjects with tetanus antitoxin concentration ≥ 1.0 IU/mL	99.2% [97.1, 99.9]	99.2% [97.0, 99.9]	1.6

Table 3: GMCs of Antibodies against Each Pertussis Antigen (ELISA-EU/mL), 30 days after Daptacel+IPV (Group A), Daptacel+Menactra (Group B), and Daptacel alone (Group C), - PPP

Ag	**Group A (N=250)** **GMC (M) [95%CI]**	**Group B (N=238)** **GMC (M) [95%CI]**	**Group C (N=121)** **GMC (M) [95%CI]**	**Upper Limit of 2-sided 95%CI of Ratio of GMCs (Group A/Group B)**
PT	70.0 (243) [63.0, 77.8]	71.0 (236) [63.8,79.0]	73.0 (117) [61.9, 86.0]	1.1
FHA	133 (246) [117, 152]	145 (237) [127,165]	131 (118) [110,156]	1.1
FIM	123 (243) [92.5, 164]	113 (238) [84.0, ,151]	95.2 (116) [60.4,150]	**1.6**
PRN	115 (247) [97.0, 136]	118 (238) [102,137]	119 (137) [107, 175]	1.2

When Menactra was co-administered with DAPTACEL, the non-inferiority criteria for the evaluation of hSBA GMT responses to meningococcal serogroups A, C, and W were met, but the criteria for serogroup Y was missed by a small margin (Table 4).

Table 4: Meningococcal Serogroup Specific hSBA GMTs and Percentage of Subjects with hSBA titers ≥1:8, 30 days after Menactra alone (Group A), Menactra+Daptacel (Group B), and Menactra+IPV (Group C), and NI Criteria Group C/Group A -PPP

Sero-Group	Group A (N=238) GMT [95%CI] (M) %≥1:8 [95%CI]	Group B (N=238) GMT [95%CI] (M) %≥1:8 [95%CI]	Group C (N=121) GMT [95%CI] (M) %≥1:8 [95%CI]	Upper Limit of 2-sided 95% CI for Ratio of GMTs (Group C/Group A)
A	6.7 [5.7, 8.0] (137) 49.6% [41.0,58.3]	10.8 [8.7, 13.3] (131) 67.2% [58.4,75.1]	10.4 [8.1,13.3] (104) 64.4% [54.4, 73.6]	2.1 -
C	3.3 [2.7, 3.9] (138) 20.3% [13.9,28.0]	8.1 [6.3, 10.5] (131) 50.4% [41.5, 59.2]	7.8 [5.8,10.7] (103) 50.5% [40.5, 60.5]	3.4 -
Y	6.5 [5.1, 8.2] (138) 44.2% [35.8,52.9]	18.1 [14.2, 22.9] (131) 80.2% [72.3, 86.6]	26.2 [20.0,34.4] (104) 88.5% [80.7, 93.9]	**5.8** -
W	8.4 [6.7, 10.6] (138) 55.1% [46.4, 63.5]	22.8 [18.5, 28.1] (131) 87.8% [80.9, 92.9]	21.7 [16.6,28.4] (104) 82.7% [74.0,89.4]	3.7 -

The observed responses to meningococcal serogroup Y and to FIM pertussis antigen are unlikely to be of clinical significance based on the review of other immunologic parameters, including hSBA GMTs and other pertussis antigen responses, respectively.

The hSBA responses to vaccine antigens in Menactra when it was administered 30 days after DAPTACEL did not meet the non-inferiority criteria for all four serogroups when compared to the hSBA response to Menactra when it was administered 30 days before DAPTACEL. This observation is unlikely to be due to chance. In contrast reduced hSBA responses to all four meningococcal serogroups were not observed after co-administration of Menactra and DAPTACEL. These findings with the sequential Daptacel and Menactra are clinically significant and suggest immune interference in the meningococcal responses when DAPTACEL is administered before Menactra. Also of note, antibody responses to Menactra when Menatra and IPOL were received at Visit 1 and DAPTACEL at Visit 2 appeared to be lower than expected based on historical data. The Applicant explained that this observation is potentially due to the use of different human complement assays (rabbit versus human), non-contemporaneous testing, and differences in the study populations (sample size, age, geography, past vaccinations, etc.).

The diminished immune response to Menactra when it is administered 30 days after DAPTACEL is a significant concern, especially in those individuals who are at high risk for meningococcal disease. In order to mitigate this risk to children who may receive both vaccines in close proximity at the time of school entry, the reviewer recommended that the Section on Drug Interactions in the Menactra and DAPTACEL package inserts include language reflecting the potential for immune interference in the meningococcal hSBA responses when Menactra is administered 30 days after DAPTACEL.

The generalizability of these findings may be limited by the study design which evaluated co-administration of the vaccines in children 4- 6 years of age. The study did not evaluate whether DAPTACEL interferes with the responses to Menactra when given to children <4 yo and in children >6yo to <11yo. It also did not evaluate the potential for interference that other DTaP containing vaccines may have on meningococcal seroresponse rates when they are administered 30 days before Menactra. Because meningococcal disease is a highly invasive, rapidly progressive, life threatening illness, vaccination must dependably confer immunity, and avoiding potential immune interference should be a primary consideration, especially in high risk individuals. Therefore the data generated from Study MTA43 may be considered relevant to other age groups and other similarly manufactured DTaP containing products.

Bioresearch Monitoring

The study was conducted at 45 clinical sites involving 28 clinical investigators and enrolling 881 subjects. CBER Bioresearch Monitoring (BIMO) issued inspection assignments for clinical sites in Columbus, Ohio; Syracuse, New York; and Little Rock, Arkansas, which together represents 14% of the total enrollees in the study. The data audit portion of the inspection focused on the verification of the safety and immunogenicity data submitted in the BLA for randomly selected subjects enrolled at these sites. The inspections did not reveal significant problems that impacted the data submitted in this marketing application.

7. SAFETY

There were no primary endpoints for safety; however, safety was evaluated as secondary (descriptive) endpoints and included 7 days post-vaccination assessment of solicited local and systemic reactions, 30 days post-vaccination assessment of unsolicited AEs, and monitoring of serious adverse events throughout the study duration. The most frequently reported solicited local reaction at either the Menactra or DAPTACEL injection site across all groups was pain, reported in 52% to 72% of subjects at the DAPTACEL site and 52% to 61% of subjects at the Menactra site. The most frequently reported solicited systemic reaction across all groups was myalgia across all study groups, reported in 25.8% to 46.2% of subjects following administration of DAPTACEL alone or with a concomitant vaccine, and in 24.2% to 37.3% subjects following administration of Menactra alone or with a concomitant vaccine. The reported rates and types of unsolicited AEs are similar to that seen in the general population for children 4 to 6 years of age. None of the three reported SAEs were considered related to study vaccination and there were no deaths reported during the study.

8. ADVISORY COMMITTEE MEETING

This supplement did not require input from Vaccines and Related Biological Products Advisory Committee.

9. OTHER RELEVANT REGULATORY ISSUES

There were no additional relevant issues.

10. LABELING

Review of the proposed changes to the PIs of Menactra and DAPTACEL identified sections which required modifications to the text. In addition, revisions to certain sections of both PIs were requested and reviewed to satisfy new PLLR labeling requirements. The following sections

of the label were revised: Section 6 (Adverse Reactions); Section 8 (Use in Specific Populations); and Section 14 (Clinical Studies). The Applicant's proposed updates to Section 5 (Warnings and Precautions) is not consistent with CFR 201.57 requirements for this section, which stipulates that information in Section 5 apply to a demonstrated safety concern, rather than immunogenicity findings suggestive of immune interference as in this case. After negotiations with the Applicant, it was determined by the review committee that the Final Draft PIs for Menactra and DAPTACEL, submitted on September 16, 2016, and September 13, 2016, respectively, were acceptable.

11. RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The committee recommends approval of the Menactra BLA supplement to include immunogenicity and safety data to support concomitant vaccination with Menactra and DAPTACEL or vaccination with Menactra 30 days prior to DAPTACEL for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135 and diseases caused by *Bordetella pertussis, Clostridium tetani,* and *Corynebacterium diphtheria* in children 4 through 6 years in the US.

b) Risk/Benefit Assessment

The benefit of co-administration of both DAPTACEL and Menactra at the same office visit prior to school entry allows for health care providers to maximize vaccination opportunities for their patient population. The safety evaluations from Study MTA43 do not demonstrate any unexpected adverse outcomes of concern. Furthermore, the concomitant administration of both vaccines at the same visit does not demonstrate immune interference with regard to the tetanus, diphtheria, pertussis and meningococcal serogroup vaccine components. Therefore, benefit-risk is favorable for co-administration DAPTACEL and Menactra. However, the diminished immune response to Menactra when it is administered 30 days after DAPTACEL is a significant concern, especially in those individuals who are at high risk for meningococcal disease. Health care providers should consider the timing of vaccination with Menactra and DAPTACEL in order to prevent sub-optimal immune response to Menactra vaccination.