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BLA Clinical Review Memorandum

Application Type	Supplemental Biologics License Application (sBLA)
STN	125111/904
CBER Received Date	December 10, 2021
PDUFA Goal Date	January 9, 2023
Division / Office	DVRPA / OVRR
Priority Review (Yes/No)	No
Reviewer Name	Nadine Peart Akindele, MD Clinical Review Staff IOD, DVRPA, OVRR, CBER
Review Completion Date / Stamped Date	January 3, 2023
Supervisory Concurrence	Anuja Rastogi, MD, MHS Branch Chief, Clinical Review Staff, IOD, DVRPA, OVRR, CBER Douglas Pratt, MD, MPH Associate Director, Medical Affairs DVRPA, OVRR, CBER
Applicant	Sanofi Pasteur, Ltd.
Established Name	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed
Trade Name	Adacel
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants	Each 0.5 mL dose contains 5 Lf tetanus toxoid (T), 2 Lf diphtheria toxoid (d), and acellular pertussis antigens [2.5 mcg detoxified pertussis toxin (PT), 5 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)], 1.5 mg aluminum phosphate (0.33 mg aluminum) as adjuvant, ≤5 mcg residual formaldehyde, <50 ng residual glutaraldehyde and 3.3 mg (0.6% v/v) 2-phenoxyethanol.
Dosage Form and Route of Administration	Suspension, intramuscular
Dosing Regimen	Single dose during 3rd trimester of pregnancy
New Indication and Intended Population	Immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
ACIP	Advisory Committee on Immunization Practices
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Review
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
DPV	Division of Pharmacovigilance
DVRPA	Division of Vaccines and Related Product Applications
FDA	US Food and Drug Administration
FHA	filamentous hemagglutinin
ICD-9	International Classification of Diseases (9th Edition)
IPV	inactivated polio vaccine
KP	Kaiser Permanente
KPVSC	KP Vaccine Study Center
LMP	last menstrual period
NCT	National Clinical Trial
OBPV	Office of Biostatistics and Pharmacovigilance
OR	odds ratio
PREA	Pediatric Research Equity Act
PRN	pertactin
PT	pertussis toxoid
RCT	randomized controlled trial
RR	relative risk
RWE	real-world evidence
SGA	small for gestational age
SLR	systematic literature review
STN	Submission Tracking Number
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed
US	United States
USPSTF	United States Preventive Services Task Force
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine effectiveness
VSD	Vaccine Safety Datalink
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Sanofi Pasteur Ltd. (Sanofi) submitted a supplemental Biologics License Application (sBLA) to support an indication for Adacel immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age.

The effectiveness of Adacel immunization during the third trimester of pregnancy to prevent pertussis among infants less than 2 months of age was based on a re-analysis of Adacel-specific data from an observational case-control study of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap) vaccine effectiveness (VE). A conditional logistic regression model controlling for age, maternal education, and family size was fit data from 81 infants who developed pertussis (5 who had been exposed to Adacel in utero and 76 who had not and 116 matched controls (19 who had been exposed to Adacel in utero and 97 who had not) resulting in a vaccine effectiveness for Adacel administration in the third trimester of 84.3% (95% CI: 24.8%, 96.7%). These data support Adacel effectiveness against pertussis in infants less than 2 months old when administered to their mothers during the third trimester of pregnancy.

The safety of Adacel administered to women during the third trimester of pregnancy (Adacel recipients, n=225; controls, n=675) was evaluated in study Td512, a post-licensure safety surveillance study evaluating the routine use of Adacel. Adacel-exposed mother-infant dyads did not experience any of the 42 unique fetal outcomes being monitored at more frequent rates compared to control mother-infant dyads.

Other supportive data provided by the Applicant includes a systematic literature review which includes data from 4 randomized control trials and 14 observational studies. Sixteen of these studies (including the randomized control trials) include data from participants who had received a Tdap-containing vaccine, the majority of whom received Adacel. Overall, these studies demonstrate an acceptable reactogenicity profile amongst women who were vaccinated with Adacel during pregnancy. No serious adverse events (SAEs) were reported among three randomized controlled clinical trials that were considered by the investigators to be related to Adacel, and this reviewer agrees with these assessments. Pregnancy outcomes including chorioamnionitis, low birth weight, small for gestational age (SGA), still birth, congenital malformations, chorioamnionitis, 5-minute Apgar scores, cord blood pH, neonatal complications or neonatal death, pre-eclampsia/eclampsia, placental disease/conditions, and cesarean delivery were not identified to be more likely after exposure to Adacel during pregnancy.

Additionally, data from the Adacel pregnancy registry revealed that after Adacel exposure during pregnancy no congenital anomaly patterns were identified in association with Adacel use during pregnancy.

In conclusion, the safety and effectiveness data in this application support a revision to the Adacel prescribing information to include the proposed indication and use.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The number of participants was too small to conduct meaningful effectiveness analyses based on race and ethnicity.

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	

Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. Clinical and Regulatory Background

Adacel was initially approved by FDA on June 10, 2005, as a single dose for active booster immunization against tetanus, diphtheria, and pertussis in individuals 11 through 64 years of age. On March 28, 2014, the approved usage was extended to include individuals as young as 10 years of age and on January 11, 2019, the dosage and administration section of the Adacel prescribing information was again revised to provide for an additional dose 8 years or more after the initial dose of a Tdap vaccine. Please see Adacel US prescribing information for additional information.

Most serious pertussis cases, hospitalizations, and deaths occur in infants less than 2 months of age who are too young to benefit from active immunization. Several measures were considered by public health officials to prevent pertussis in young infants and early recommendations were directed at preventing pertussis by assuring vaccination of close contacts of newborn infants in a strategy termed “cocooning”; this approach was met with limited success in controlling pertussis in infants.

In 2011, in an effort to further reduce the increased burden of pertussis in infants observed in previous years, the Advisory Committee on Immunization Practices (ACIP) and the Centers for Disease Control and Prevention (CDC) recommended that unvaccinated pregnant women receive a dose of a Tdap vaccine (CDC, 2011). In 2012, ACIP made recommendations to extend the use of Tdap vaccines during the third trimester of each pregnancy; the updated recommendation was published in the *Morbidity and Mortality Weekly Report* in 2013, and subsequently implemented.

CDC recommendations for use of Tdap vaccines during pregnancy were not inconsistent with the existing prescribing information for Adacel as there are no contraindications to use of Adacel during pregnancy. However, the safety and effectiveness of Adacel for prevention of pertussis in the infants of individuals vaccinated during pregnancy through passive immunization have not previously been addressed in the prescribing information. With this BLA supplement the Applicant submitted data intended to support the use of Adacel when administered to pregnant individuals for prevention of pertussis in their infants less than 2 months of age, and revisions to the relevant sections of the prescribing information.

2.1 Disease or Health-Related Condition(s) Studied

Pertussis disease, caused by the bacterium *Bordetella pertussis*, is a highly contagious respiratory illness affecting all age groups. The morbidity associated with pertussis is highest in infants <6 months of age; in 2021, the highest incidence of reported pertussis cases in the US was in infants <6 months of age, with 3.6 cases/per 100,000 infants, of which 31% were hospitalized (CDC, 2021a). The case fatality rate for pertussis among infants younger than six months of age was approximately 1%, with the majority of deaths occurring in those younger than two months of age (CDC, 2021a).

The most common complications of pertussis infection in infants include apnea, pneumonia, and weight loss secondary to feeding difficulties and post-tussive vomiting. Other complications include seizures and encephalopathy.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Management of infant pertussis infection includes antimicrobial therapy and supportive care. Preventive measures include age-appropriate immunization against pertussis for infants, children, adolescents, adults, and unimmunized/partially immunized close contacts of the index case.

2.3 Safety and Efficacy of Pharmacologically Related Products

Boostrix (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed; GlaxoSmithKline Biologicals) is approved by the FDA for active booster immunization against tetanus, diphtheria and pertussis for persons 10 years of age and older and for immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age. Please see the Boostrix US prescribing information.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Please see section 6.2 of the Adacel US prescribing information regarding adverse events (AEs) identified during post-approval use of Adacel worldwide.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

January 25, 2021, Type C meeting
Written communication was provided to the Applicant regarding the data considered acceptable to support a claim of vaccine effectiveness or to support changes to the prescribing information including the utilization of a study conducted by the CDC (Skoff, et al., 2017) in which the elements needed to support a change might be available.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICE

3.1 Submission Quality and Completeness

The application was considered acceptable for filing. However, multiple information requests were communicated to the Applicant to clarify, verify, and update the dataset used for Td500059 analyses to support the effectiveness evaluation. See sections 4 and 5.2 for additional details.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Study Td500059 incorporated data from existing datasets and published data and study Td512 did not have clinical sites that actively collected data. Due to the lack of clinical sites that collected new data to be inspected, the CBER Bioresearch Monitoring reviewer recommended a waiver of clinical site inspections for both studies and the Review Committee concurred with this recommendation. Following review of the study reports, no deficiencies were identified that would affect the integrity of the clinical data submitted in this sBLA.

3.3 Financial Disclosures

For the CDC case-control study (Skoff, et al., 2017), the 11 authors who were also study investigators at the Emerging Infection Program Network sites reported no conflicts of interest or financial relationships relevant to the study. Sanofi study Td500059 was a re-analysis from the CDC study dataset.

Covered clinical study: The Applicant provided financial disclosures for study investigators participating in studies Td500059 and Td512.
Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from applicant)
Total number of investigators identified: Td500059: 38; Td512: 3
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Applicant of covered study: _____ Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

This submission did not require CMC review.

4.2 Assay Validation

This submission did not require assay validation.

4.3 Nonclinical Pharmacology/Toxicology

This submission contained no new or updated pre-clinical information.

4.5 Statistical

The statistical reviewer confirmed the results submitted by the Applicant. The statistical methodology used in the context of an observational case-control study was found to be adequate.

Based on Td500059 main and sensitivity analyses performed by the Applicant, the statistical reviewer concluded that, overall, Adacel was statistically likely to be effective for the intended indication, and the results were robust to the analysis methods and missing data. Td500059 analyses had some limitations, since the re-analyses were performed post hoc and based on data from a retrospective case-control study (Skoff, et al., 2017), and had limited study power. Please see CBER statistical review memorandum for further details about the statistical methods.

4.6 Real-World Evidence

The review of study Td500059 was also conducted by the CBER OBPV/RWE reviewer who determined that the evaluation of the data subset in this report appears acceptable. Additionally, the RWE reviewer reviewed the Applicant's submission of 4 randomized controlled trials conducted using Adacel in pregnant women. The RWE reviewer determined that although the 4 VE studies are not robust, they provide supportive information regarding the VE of maternal immunization with Adacel at preventing pertussis in infants < 2-3 months. Please see CBER RWE reviewer memorandum for additional information.

4.7 Pharmacovigilance

The review of Td512 and the Adacel pregnancy registry was also conducted by the CBER OBPV/DPV reviewer.

Regarding study Td512, the reviewer concluded that this was a claims-based observational study with limited safety data; however, the reviewer agreed with the Applicant assessment that there were no overall increased rates of maternal and fetal adverse outcomes compared to controls in study Td512.

Regarding the pregnancy registry, the reviewer concluded that the registry data demonstrated a substantial heterogeneity of maternal and infant outcomes, with no safety risk identified for Adacel exposure in any trimester of pregnancy. The reviewer also noted that the background prevalence rates for other maternal complication such as pre-eclampsia, gestational diabetes, gestational hypertension, premature rupture of membranes, and premature labor and delivery may account for the reporting of such events in the patients vaccinated with Adacel and that the number of reported events does not seem to exceed the rates in the general population. Additionally, the reviewer evaluated the current VAERS data and concluded that there were no new safety concerns.

In summary, the DPV reviewer determined that based on the available data no specific risks have been identified in conjunction with Tdap vaccine exposure during pregnancy and that the pharmacovigilance plan to continue pregnancy registry and provide interim analyses in periodic safety reports is acceptable. The reviewer did not recommend a Risk Evaluation and Mitigation Strategy or a safety post-marketing requirement or post-marketing commitment study.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This sBLA contains results from study Td500059, a re-analysis of a CDC case-control study, and reports from study Td512, a post-licensure surveillance study. Td500059 was the main study intended to support effectiveness of Adacel when administered during the 3rd trimester of pregnancy. Study Td512 supported the safety of Adacel administered to women during pregnancy, and neonatal outcomes. Safety of Adacel use in pregnancy was additionally supported by a summary of the Adacel pregnancy registry and a systematic literature review and a review of Vaccine Adverse Event Reporting System (VAERS) data.

5.2 BLA Documents That Serve as the Basis for the Clinical Review

The following amendments were reviewed in support of this application:
Amendment 0

- Module 1, all sections: Administrative information and prescribing information
- Module 2, sections, 2.5 clinical overview, 2.7 summaries of clinical efficacy and safety, synopses of individual studies
- Module 5, sections 5.2 tabular listing of all clinical studies, section 5.3 clinical study reports, section 5.4 literature references

Responses to CBER information requests included the following:

- Amendment 1- financial disclosures, carton and container
- Amendment 2- reports of post-marketing experience
- Amendment 3- response to deficiencies
- Amendment 4- pharmacovigilance plan
- Amendment 5- pregnancy registry
- Amendment 6- letter of authorization to CDC for Master File
- Amendment 7- further details on systematic literature review
- Amendment 8- Td500059 study report for evaluation of relevance and reliability of data
- Amendment 10-updated risk management plan

5.3 Table of Studies/Clinical Trials

Table 1. Study Information

Study ID #/ Location/ NCT #	**Description and Pertinent Study Objectives**	**Adacel N**	**Comparator N**
Vaccine effectiveness study: Td500059 NCT05040802	Re-analysis of data collected from a case-control study. Td500059 primary objective: to determine the effectiveness of Adacel against pertussis disease in infants <2 months when administered during pregnancy following the current ACIP recommendations, i.e., from 27 to 36 weeks of gestation, and 14 days or more before delivery.	Infants: 160	Infants: 302
Safety study: Td512 NCT00258882	A descriptive, epidemiological surveillance study using a large healthcare organization to identify any risks or uncommon events associated with the use of Adacel. The results from the sub-group of pregnant women were analyzed.	Women: 225	Women: 676

Source: Adapted from STN 125111/904 Amendment 0 Section 5.2 Tabular Listings of all Clinical Studies Table 1

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

There were no issues or concerns identified in this sBLA that would have benefitted from a vaccines advisory committee discussion.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed

5.5.1 References

Centers for Disease Control and Prevention (CDC) (2011). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months --- Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR. Morbidity and mortality weekly report*, *60*(41), 1424–1426. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6041a4.htm. Accessed September 19, 2022.

CDC (2021a). 2021 Provisional pertussis surveillance report. https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2021_provisional.pdf. Accessed September 19, 2022.

DeSilva, M., Vazquez-Benitez, G., Nordin, JD, et al. (2017). Maternal Tdap vaccination and risk of infant morbidity. *Vaccine*, *35*(29), 3655–3660. https://doi.org/10.1016/j.vaccine.2017.05.041

Donegan K, King B, Bryan P. (2014). Safety of pertussis vaccination in pregnant women in UK: observational study *BMJ* 2014; 349 :g4219 doi:10.1136/bmj.g4219

Halperin, SA, Langley, JM, Ye, L, et al. (2018). A Randomized Controlled Trial of the Safety and Immunogenicity of Tetanus, Diphtheria, and Acellular Pertussis Vaccine Immunization During Pregnancy and Subsequent Infant Immune Response. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, *67*(7), 1063–1071. https://doi.org/10.1093/cid/ciy244

Hoang, HT, Leuridan, E, Maertens, K, et al. (2016). Pertussis vaccination during pregnancy in Vietnam: Results of a randomized controlled trial Pertussis vaccination during pregnancy. *Vaccine*, *34*(1), 151–159. https://doi.org/10.1016/j.vaccine.2015.10.098

Kharbanda, EO, Vazquez-Benitez, G, Lipkind, H. S, et al. (2014). Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. *JAMA*, *312*(18), 1897–1904. https://doi.org/10.1001/jama.2014.14825

Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. (2016). Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007-2013. *Vaccine*. 2016 Feb 10;34(7):968-73. doi: 10.1016/j.vaccine.2015.12.046. Epub 2016 Jan 4. PMID: 26765288; PMCID: PMC6506839.

Morgan, J L, Baggari, SR, McIntire, DD, & Sheffield, JS. (2015). Pregnancy outcomes after antepartum tetanus, diphtheria, and acellular pertussis vaccination. *Obstetrics and gynecology*, *125*(6), 1433–1438. https://doi.org/10.1097/AOG.0000000000000862

Moro, PL, Cragan, J, Tepper, N, et al. (2016). Enhanced surveillance of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines in pregnancy in the Vaccine Adverse Event Reporting System (VAERS), 2011-2015. *Vaccine*, *34*(20), 2349–2353. https://doi.org/10.1016/j.vaccine.2016.03.049

Munoz, FM, Bond, NH, Maccato, M, et al. (2014). Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. *JAMA*, *311*(17), 1760–1769. https://doi.org/10.1001/jama.2014.3633

Skoff, TH, Blain, AE, Watt, J. et al. (2017). Impact of the US Maternal Tetanus, Diphtheria, and Acellular Pertussis Vaccination Program on Preventing Pertussis in Infants <2 Months of Age: A Case-Control Evaluation. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *65*(12), 1977–1983. https://doi.org/10.1093/cid/cix724. Accessed September 19, 2022.

Villarreal Pérez, JZ, Ramírez Aranda, JM, de la O Cavazos, M, et al. (2017). Randomized clinical trial of the safety and immunogenicity of the Tdap vaccine in pregnant Mexican women. *Human vaccines & immunotherapeutics*, *13*(1), 128–135. https://doi.org/10.1080/21645515.2016.1232786

Zheteyeva, YA, Moro, PL, Tepper, NK, et al. (2012). Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. *American journal of obstetrics and gynecology*, *207*(1), 59.e1–59.e597. https://doi.org/10.1016/j.ajog.2012.05.006

5.5.2 Review of Systematic Literature Review

To comprehensively address the effectiveness and safety of Adacel use in pregnant women for infants <2 months of age, the Applicant provided a Systematic Literature Review (SLR) on vaccine effectiveness and safety (pregnancy and neonatal outcomes) associated with use of US and non-US formulations of Adacel. The SLR is entitled:

> TD500065 - Systematic Literature Review to Assess the Effectiveness, Immunogenicity, and Safety of Adacel/Adacel-Polio in Pregnancy, Study Period: Literature published between 01 January 1995 and 06 March 2018, Report date: Final SLR report version 1.0 06 June 2022

In a January 2021 communication, the FDA informed the Applicant that an SLR may not be used as evidence for a claim of vaccine effectiveness or to support changes to the prescribing information but may be considered supportive when supplementing a primary source of data to increase robustness of the evidence.

Please see the Real-World-Evidence (RWE) reviewer memorandum for a summary of the methods of the review as well as the overview of vaccine effectiveness from the literature review. This memorandum will summarize the SLR safety data submitted by the Applicant.

Table 2. Characteristics of Studies Assessing the Safety of Tdap Maternal Immunization (Studies Including Adacel and Unspecified Vaccine Brands)

Authors and Country	Setting/Data Sources	Study Design/ Period	Study Population	Intervention/ Comparison	N Intervention Group	N Control Group	Outcomes
Munoz *et al*., 2014; USA	3 National Institutes of Health Vaccine Treatment Evaluation Unit sites	RCT (double blind, randomized placebo-controlled, crossover trial); 2008-2012	Women 18-45 years of age in the 30th-32nd week of a pregnancy at low risk for complications	Adacel Placebo: 0.9% saline Solution	48 (Group 1: 33 pregnant women who received Adacel at 30–32 weeks of gestation and saline postpartum Group 2: 15 pregnant women who received saline at 30–32 weeks of gestation and Adacel postpartum	32 (nonpregnant age-matched controls who received Adacel)	Pregnant women: Solicited, unsolicited reactions, SAEs, and pregnancy outcomes
Villarreal Pérez *et al*., 2017; Mexico	12 outpatient health centers of the Nuevo León Health Services	RCT, Double-blind, parallel group 2011-2014	Pregnant women 18-38 years of age with low obstetric risk and normal anatomical ultrasound at 24–26 weeks gestation	Adacel Placebo: 0.9% saline Solution	90	81	Pregnant women: Solicited, unsolicited reactions, and pregnancy outcomes
Halperin *et al*., 2018; Canada	Multicenter	RCT, Observer blinded, 2007-2011, 2012-2014	Pregnant women 18-45 years of age immunized with Adacel or Td at 34-35 weeks of gestation	Adacel Td Adsorbed	135	138	Pregnant women: Solicited, unsolicited reactions, SAEs and pregnancy outcomes

Authors and Country	Setting/Data Sources	Study Design/ Period	Study Population	Intervention/ Comparison	N Intervention Group	N Control Group	Outcomes
Hoang *et al.,* 2016; Vietnam	Multi-center	RCT, 2013	Pregnant women immunized with Adacel or TT	Adacel Tetanus Toxoid	52	51	Pregnant women: Solicited, unsolicited reactions, SAEs and pregnancy outcomes
Zheteyeva *et al*., 2012; USA	VAERS	Observational Retrospective cohort, 2005-2010	Pregnant women immunized with Tdap	Adacel (72%) Tdap3 (15%) Unknown (13%)	132	--	Pregnant women: Obstetric, perinatal and neonatal outcomes
Donegan *et al*., 2014 ; England	Clinical Practice Research Datalink (CPRD) data	Observational retrospective analysis, 2012-2013	Pregnant women for whom at least 28 days of follow-up data after vaccination was available	Adacel-Polio	6185	18, 523 (matched historical unvaccinated pregnant women)	Pregnant women: Pregnancy and infant outcomes
Kharbanda *et al*., 2014; USA	Vaccine Safety Datalink (VSD) sites (2 sites) Analysis of health insurance-based electronic health records	Observational retrospective cohort, 2010–2012	Pregnant women with singleton live births immunized with Tdap	Adacel (≥80%[a])	26,229	97,265 (women who did not receive Tdap in pregnancy)	Pregnant women: Chorioamnionitis

Authors and Country	Setting/Data Sources	Study Design/ Period	Study Population	Intervention/ Comparison	N Intervention Group	N Control Group	Outcomes
Moro *et al.*, 2016	VAERS	Observational retrospective, 2011-2015	Tdap administered during pregnancy	Adacel (59.7%) Tdap3 (33.2%) Unknown (7.1%)	524	--	Pregnant women: Injection related reactions and pregnancy outcomes
Kharbanda *et al.*, 2016 USA	VSD data (7 sites)	Observational retrospective, 2007-2013	Pregnant women with singleton live births immunized with Tdap	Adacel (≥80%[a])	53,885	109,253 (matched unvaccinated pregnant women)	Pregnant women: Medically attended events
Morgan *et al*., 2017; USA	Parkland Hospital database of pregnancy, delivery, and neonatal records	Observational retrospective cohort, 2013–2014	Pregnant women who were offered Adacel immunization	Adacel[a]	7152	226 (women who declined vaccination)	Pregnant women: Chorioamnionitis
DeSilva *et al*., 2017; USA	VSD data (7 sites)	Observational retrospective cohort, 2010–2013	Women who were continuously insured from 6 months prior to their last menstrual period through 6 weeks postpartum, with 1 outpatient visit during pregnancy.	Adacel (≥80%[a])	45,008	152,556 (unvaccinated pregnant women)	Pregnant women: Chorioamnionitis and other neonatal outcomes
Perry *et al*., 2017, USA	Single-center	Prospective observational, 2014-2016	Pregnant women recruited at the time of Tdap administration	Adacel (74.1%[a]) Tdap3 (25.9%)	737	--	Pregnant women: Injection-site reactions

Authors and Country	Setting/Data Sources	Study Design/ Period	Study Population	Intervention/ Comparison	N Intervention Group	N Control Group	Outcomes
Talbot *et al*., 2010; USA	Single-center	Observational, 2006	Unintentionally immunized pregnant health care worker	Adacel	16	--	Pregnant women: Injection related and systemic reactions
Morgan *et al*., 2015, USA	Parkland Hospital database of pregnancy, delivery, and neonatal records	Observational retrospective cohort	Infants of women who received Adacel on or after 23 weeks gestation	Adacel[a]	7152	226 (infants of mothers who declined Tdap vaccination)	Infants: Neonatal outcomes
Sukumaran *et al*., 2015; USA	VSD data (7 sites)	Observational retrospective, 2007-2013	Pregnant women who received Tdap and inactivated influenza vaccine concomitantly	Adacel (≥80%[a])	8,464	28,380 (women who received Tdap and inactivated influenza vaccine sequentially)	Concomitant use and repeat doses: Injection-related reactions and pregnancy outcomes
Sukumaran *et al*., 2019; USA	VSD data	Observational retrospective	Women immunized with Tdap in pregnancy	Adacel (≥80%[a])	4,812: <2 years following receipt of a tetanus-containing vaccine 9,999: 2-5 years following receipt of a tetanus-containing vaccine	14,344 (>5 years following the receipt of a tetanus-containing vaccine	Concomitant use and repeat doses: Injection site, systemic and allergic reactions

Authors and Country	Setting/Data Sources	Study Design/ Period	Study Population	Intervention/ Comparison	N Intervention Group	N Control Group	Outcomes
Sukumaran *et al*., 2019; USA	VSD data	Observational retrospective	Singleton infants born to mothers immunized with Tdap in pregnancy	Adacel (≥80%[a])	3,313: <2 years following receipt of a tetanus-containing vaccine 7,226: 2-5 years following receipt of a tetanus-containing vaccine	10,633: (>5 years following the receipt of a tetanus-containing vaccine	Concomitant use and repeat doses: Neonatal outcomes
Regan *et al*., 2016; Australia	WA Health immunization database	Prospective observational cohort	Women who had received Tdap and trivalent inactivated influenza vaccine (TIV)	Adacel (76.9%) Tdap3 (23.0%) TIV	1257: received Tdap exclusively 1,506: received Tdap and TIV concomitantly	1,584: received TIV exclusively	Concomitant use and repeat doses: Injection site and systemic reactions

Source: Adapted from STN 125111/904 amendment 0, Summary of Clinical Safety, Tables 7.1, 7.2, 7.3
RCS=retrospective cohort study; RCT=Randomized Controlled Trial; TIV=trivalent influenza vaccine; Tdap3=Boostrix (GlaxoSmithKline)
a. Communication between Applicant and study investigator occurred to confirm the proportion of Adacel recipients

TD500065 Safety results

For safety, the inclusion criteria for the safety studies were broader than the approach taken for the immunogenicity and effectiveness studies. Studies included in the SLR of safety provided data for other Tdap brands in addition to Adacel or Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine (Tdap-IPV, Adacel-Polio, Sanofi Pasteur, Canada), as well as studies in which the Tdap vaccine used was unknown. In total, 18 publications were identified that assessed safety after Tdap vaccination. Twelve of these studies were studies with known Tdap vaccine brand usage and 6 were observational studies where the Tdap vaccine brand was unspecified. The Applicant took steps to confirm the Tdap vaccine brand used when possible, resulting in 16 studies in which Adacel or Adacel-Polio was used in >50% of participants (Table 2).

*R*andomized Controlled Trials

There were 4 studies with United States Preventive Services Task Force (USPSTF) Evidence Level of I. There were 3 studies with USPSTF Evidence Quality of "Good". These studies were four randomized controlled trials (RCTs): Munoz, et al. 2014; Halperin, et al. 2018; Villarreal Pérez, et al. 2017; and Hoang, et al. 2016.

All four studies demonstrated similar rates of solicited local reactions between Adacel recipients and the comparator arms. The most common reactions following Adacel administration were injection site reactions. Munoz, et al. reported that approximately 80% of women who received Adacel while they were pregnant or immediately postpartum, and nonpregnant women reported injection site reactions (pain, erythema/redness, or induration/swelling). Injection site pain was reported in the Halperin, et al. study by over 80% of pregnant women who received Adacel or Td Adsorbed vaccine during pregnancy. In the study reported by Villarreal Pérez, et al., the percentage of pregnant women reporting mild local pain at 24 and at 48 hours after vaccination with Adacel during pregnancy (22.2% and 7.8%, respectively) was similar in women who received a placebo injection during pregnancy (21.0% and 6.2%, respectively).

In the RCT conducted by Munoz, et al., non-serious AEs occurred in 63.6% (95% CI: 45.1%, 79.6%) of women given Adacel during pregnancy and 28.1% (95% CI: 13.7%, 46.7%) of nonpregnant women who received Adacel. A higher rate of SAEs was observed when recipients who received Adacel during pregnancy were compared to nonpregnant women who received Adacel (21% vs. 3.1%). These included hypertension, pancreatitis, and appendicitis among pregnant women who received Adacel and pelvic fracture after a motor vehicle accident in those who received placebo. All SAEs occurred >30 days post-vaccination. No SAEs were judged by the investigators to be attributable to Adacel. With regard to pregnancy outcomes, adverse outcomes were reported by 4 (12%) women who received Adacel during pregnancy: preterm contractions, wound hematoma after cesarean, hypertension, and fetal distress (USPSTF Evidence Level/Quality: I/Good).

The RCT conducted by Villarreal Pérez, et al. demonstrated no statistically significant differences regarding solicited reactions between Adacel recipients and placebo recipients and SAEs were not reported by the study authors (USPSTF Evidence Level/Quality: I/Good).

Halperin, et al. conducted a comparative RCT evaluating safety of Adacel as compared to tetanus-diphtheria toxoids, adsorbed (Td adsorbed, Sanofi Pasteur Ltd., Canada). Mild fatigue and muscle aches were less common in Adacel recipients than Td recipients (fatigue: 13.3% vs. 23.4%; muscle aches 4.4% vs. 20.4%), though severe muscle aches were more common in

Adacel recipients (4.4% vs. 0%). SAEs occurred at similar rates between Adacel and Td recipients (4.4% vs. 5.8%) and none were considered related to study vaccination by the investigators. Serious complications of pregnancy/labor also occurred at similar rates between Adacel and Td recipients (5.9% vs. 6.5%) and 1 in the Adacel group was assessed by investigator as possibly related (gestational hypertension) as compared to 3 in the Td group (pre-eclampsia, premature delivery, and HELLP syndrome [hemolysis, elevated liver enzymes, low platelet count]) (USPSTF Evidence Level/Quality: I/Good).

No significant differences in safety parameters measured were found between groups in the RCT conducted by Hoang, et al., which compared Adacel and tetanus toxoid (TT, Sanofi Pasteur, Canada) administered during pregnancy. There were 4 SAEs (fever, n=1; fatigue, n=1; premature contractions, n=2) reported in the Adacel group and 2 SAEs (premature contractions, n=1; preterm delivery with stillbirth, n=1) in the TT group. All premature contractions occurred more than 1 month after vaccination and the preterm delivery with stillbirth at 7 months gestation occurred 5 weeks after tetanus toxoid vaccination. None of the reported SAEs were reported by the authors to have a causal relationship with study vaccination (USPSTF Evidence Level/Quality: I/Fair).

Observational studies
The other observational and cohort studies assessed pre-defined maternal and infant outcomes for pregnant women who received Tdap or Tdap-IPV vaccine (including non-Sanofi products) during pregnancy and showed that there was no difference in these outcomes compared with pregnant women who did not receive a Tdap containing vaccine during pregnancy. Maternal and infant outcomes evaluated in these studies included preterm delivery or SGA birth and chorioamnionitis (Kharbanda, et al. 2014), gestational diabetes or hypertension (Kharbanda, et al. 2016), still birth, congenital malformations, chorioamnionitis, 5-minute Apgar, cord blood pH, neonatal complications or neonatal death (Morgan, et al. 2015), pre-eclampsia/eclampsia, placental disease/conditions, cesarean delivery (Donegan, et al. 2014).

In study Kharbanda, et al. 2014, which utilized the Vaccine Safety Datalink (VSD), a small but statistically significant increased risk of being diagnosed with chorioamnionitis among women who received Tdap vaccine at any time during pregnancy was shown, with an adjusted relative risk (RR) = 1.19 [95% CI: 1.13, 1.26] (6.1% of Tdap-exposed women compared to 5.5% of unexposed women) and in women vaccinated between 27 and 36 weeks of gestation with an adjusted RR = 1.11 [95% CI: 1.03, 1.21]. DeSilva, et al. 2017 conducted a study to re-evaluate this risk in the VSD, and reported that chorioamnionitis was recorded in 6.4% of women who received Tdap vaccination any time during pregnancy and 5.2% of women who did not (adjusted RR [95% CI]: 1.23 [1.17, 1.28]) but did not reveal an increased risk for infant outcomes (transient tachypnea of the newborn, neonatal sepsis, neonatal pneumonia, respiratory distress syndrome, and newborn convulsions) associated with the maternal cases of chorioamnionitis.

Vaccine Adverse Event Reporting System (VAERS) data from 132 reports of Tdap vaccine administered to pregnant women (77.3% in the first trimester) prior to the ACIP recommendations on Tdap vaccination during pregnancy was reported by Zheteyeva, et al. 2012. The most frequent pregnancy-specific outcome was spontaneous abortion in 22 (16.7%) reports and one report with a major congenital anomaly (gastroschisis) was identified. VAERS data from 392 reports of Tdap vaccine administered to pregnant women (79% in the third trimester) after the ACIP recommendations was reported by Moro, et al. 2016, and revealed 1 neonatal death and no maternal deaths. The most frequent pregnancy-specific outcome was

oligohydramnios in 12 (3.1%) reports followed by stillbirth and preterm delivery in 11 (2.8%) reports each. The authors reported that they did not identify any concerning patterns in maternal, infant, or fetal outcomes and concluded that no new or unexpected vaccine AEs were noted among pregnant women who received Tdap vaccine after routine recommendations for maternal Tdap vaccination.

In publications where the brand of Tdap vaccine was unspecified, safety outcomes were similar to those presented for the studies with Adacel.

In summary, this systematic and comprehensive review of available literature included safety data from 18 studies, including 4 randomized controlled trial and 14 observational studies, based on data from over 1 million pregnancies. Additionally, observational studies detected a small but statistically significant increased risk of chorioamnionitis among women who received Tdap vaccine at any time during pregnancy. No conclusive association of any adverse outcome with Adacel vaccination during pregnancy was found for the mother or infant. However, these overall reassuring findings also do not demonstrate conclusively that Adacel vaccination is not causally associated with AEs of pregnancy due to small numbers of participants in the randomized trials and inherent limitations of observational study designs.

In conclusion, the results of this comprehensive literature review are consistent with the Applicant's statement that the evidence currently available supports the safety for both the women vaccinated with Adacel during their pregnancy and their infants.

Immunogenicity results

In the RCTs reported by Munoz et al., Villarreal Pérez et al., Halperin et al., and Hoang et al., pertussis specific-antibody levels were evaluated in infants born to mothers immunized with Adacel or a comparator that did not contain pertussis antigen.

All four RCTs reported higher antibody levels against all measured pertussis specific-antigens in the cord blood of infants born to women vaccinated with Adacel during pregnancy as compared to those of infants born to women vaccinated with comparator vaccines, placebo, or those not vaccinated during pregnancy. The studies had varied results for the levels of pertussis-specific antibody after the infant initiated the primary series with a Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) containing vaccine.

Halperin et al. studied a non-US licensed DTaP vaccine Pediacel (Sanofi Pasteur, Toronto, Ontario, Canada), administered to infants, according to schedule at 2, 4, 6, and 12 months of age. At 2 months of age, prior to receipt of Pediacel, infants whose mothers received Adacel in the third trimester (N=118) had higher levels of all measured pertussis specific-antibody levels (Anti-PT, anti-PRN, anti-FHA, and anti-FIM) at 2 months of age as compared to a comparator arm of infants whose mothers received a non-pertussis containing vaccine in the third trimester (Td, N=131). After completion of 3 of 4 doses of the Pediacel primary series, levels of antibody were lower for anti-PT, anti-FHA, anti-PRN, and anti-FIM for infants born to mothers who received Adacel as compared to the comparator group. After receipt of the fourth dose of the Pediacel, antibody levels in these infants for anti-PT, anti-FHA, and anti-FIM antibody measured at 13 months were lower in the Adacel group (N=115) as compared to the Td group (N=124), although 95% confidence intervals of the anti-PT levels did overlap (Adacel, 55.6 [95% CI: 48.1, 64.2]; Td, 70.2 [95% CI: 61.9, 79.6]).

In the study by Munoz et al., infants received Pentacel (DTaP, Sanofi Pasteur Inc., Swiftwater, PA) at 2, 4, 6 and 12 months of age. Antibody responses measured at 7 months of age among infants born to mothers who had received Adacel (N=33), after completion of 3 of 4 doses of the primary series of Pentacel revealed numerically lower levels of anti-PT, anti-FHA, anti-PRN, and anti-FIM as compared to infants whose mothers had received placebo in the third trimester (N=15). After completion of a 4th dose of Pentacel administered earlier than recommended, at 12 months of age, anti-PT, anti-FHA, and anti-FIM antibody levels were numerically lower in the Adacel group as compared to the comparator group. This study was limited by a small number of participants with resultant wide and overlapping 95% CIs between groups.

Villareal Pérez et al. did not report the name of the DTaP vaccine used, though reported that infants received a DTaP vaccine at 2, 4, and 6 months of age. In this study, the authors observed higher anti-PRN antibody levels at 2, 4, and 6 months of age among infants born to mothers who received Tdap during the third trimester (N=90) as compared to those who were born to mothers who received placebo in the third trimester (N=81), while anti-PT antibody levels were higher at 2 months of age, but lower at 4 and 6 months of age in the Adacel group as compared to the comparator group.

Hoang et al. reported that infants in the study received the non-US licensed hexavalent vaccine, Infanrix hexa (GSK Biologicals, Belgium) that included the following vaccine antigens: DTaP, inactivated poliovirus, hepatitis B surface antigens and *Haemophilus influenzae* type B polysaccharide. The authors found that 1 month after vaccination with 3 doses administered before 6 months of age, anti-PT antibody levels and anti-FHA antibody levels in infants in born to mothers who received Adacel during the third trimester (N=52), were similar to those among infants born to mothers who received a non-pertussis containing vaccine (monovalent tetanus vaccine, TT-VAC, Institute of Vaccines and Medical Biologicals [IVAC], Vietnam) during the third trimester (N=51) , but anti-PRN antibody levels were lower in the study group infants when compared to the comparator group.

In conclusion, published studies have reported diminished immune responses to pertussis antigens in DTaP-containing vaccines administered to infants whose mothers received Adacel during the third trimester of pregnancy compared with infants whose mothers did not receive Adacel during the third trimester of pregnancy (Halperin et al., Munoz et al.). Whether the diminished immune responses observed in vaccinated infants whose mothers received Adacel during pregnancy result in diminished effectiveness of pertussis vaccination in infants is unknown.

5.6 Adacel Pregnancy Registry

The Adacel pregnancy registry is a passive surveillance program with voluntary reporting. It was initiated in June 2005 to capture Adacel exposure during pregnancy at the request of the US FDA with the initial approval of Adacel. The goals of the registry are to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with Adacel or the non-US licensed Adacel equivalent during pregnancy. The registry follows pregnancies on an ongoing basis with descriptive analyses conducted at regular intervals for periodic safety reports. The countries included in the registry are: United States, Argentina, Australia, Belgium, Brazil, Canada, Colombia, Germany, Israel, Italy, Korea, Mexico, New Zealand, Peru, Philippines, Portugal, Romania, Spain, South Africa, Slovenia, Taiwan, Thailand, Venezuela, and Vietnam. The Applicant estimates that between June 10, 2005, and the March 16, 2022, data lock point, there have been 1,938 cases of vaccination with Adacel during pregnancy reported to the pregnancy registry.

Reviewer comment:
Initially, a data lock point of March 16, 2021, was used and the total number of cases reported in the registry were 1,840. In a response to an information request (IR) from CBER, the Applicant submitted additional data from the pregnancy registry to provide more recent data (i.e., using a data lock point closer to the time of BLA submission). With a data lock point of March 16, 2022, an additional 98 cases were added, resulting in 1,938 total cases of Adacel exposure in pregnancy within either 30 days of their LMP or during pregnancy reported to Sanofi. The data below reflects the information provided in the IR. Please see OBPV/DPV reviewer memorandum for complete review of the data from the pregnancy registry.

Table 3. Sources of Tdap Exposure Throughout Pregnancy Identified in the Adacel Pregnancy Registry

Adacel Exposure: Within 30 Days Before LMP to During Pregnancy	**N=1938**
Health Care Professionals	1310 (67.6%)
Studies sponsored by Sanofi	286 (14.8%)
Studies not sponsored by Sanofi	130 (6.7%)
Consumers	11 (0.6%)
Health Authorities	91(4.7)
Literature	11 (0.6%)
Within the US	1617 (83.4%)

Source: BLA 125111/904 Amendment 5 The Pregnancy Registry Interim report, Section 5

Women included in the registry were 12 to 54 years of age and were most commonly reported to be 25 to 34 years of age (898 women, 46.3%). Of those with known timing of administration, women were most commonly vaccinated in their third trimester (431 women, 46.3%); however, timing of exposure was unknown in 1,007 (52.0%).

Of the 1,938 cases of Adacel exposure reported, the outcome was not reported in 1,310 cases (67.6%) (including ongoing pregnancies). Outcomes were known in 628 cases (32.6%). Among the cases with known outcomes, the trimester of exposure to Adacel was known in 386 cases. For the remaining 242 cases, the information pertaining to the trimester exposure was not available. Out of all known outcomes (N=628), delivery of a normal baby occurred in 499 cases (79.4%).

Table 4. Known Pregnancy Outcomes in the Adacel Pregnancy Registry

Pregnancy Outcome	**n/N (%)**
Available known outcomes (entire cohort)	628/628 (100%)
Trimester of exposure known	386/628 (61.5%)
Delivery of a child	516/628 (79.4%)
Normal baby	499/628 (79.5%)
Congenital anomaly	17/628 (2.7%)
Death within 30 days of birth	1/628 (0.2%)
Interruption of pregnancy[a]	112/628 (17.8%)
Ectopic pregnancy	3/112 (2.7%)
Voluntary termination of pregnancy	42/112 (37.5%)
Spontaneous abortion (<20 weeks)[b]	46/112 (41.1%)
Nature of termination unknown	1/112 (0.9%)
Late fetal deaths (≥20 weeks)	16/112 (14.3%)

Pregnancy Outcome	n/N (%)
First trimester exposure outcomes	160/628 (25.5%)
Delivery of a child	120/160 (75.0%)
Normal baby	118/160 (73.8%)
Congenital anomaly	2/160 (1.3%)
Interruption of pregnancy	41/160 (25.6%)
Ectopic	2/160 (1.3%)
Voluntary termination	14/160 (8.8%)
Spontaneous abortion (<20 weeks)[c]	23/160 (14.4%)
Late fetal deaths (≥20 weeks)	2/160 (1.3%)
Second trimester exposure outcomes	71/628 (11.3)
Delivery of a child	71/71 (100%)
Normal baby	69/71 (97.2%)
Congenital anomaly	2/71 (2.8%)
Third trimester exposure outcomes	155/628 (24.7%)
Delivery of a child	149/155 (96.1%)
Normal baby	130/155 (83.9%)
Congenital anomaly	8/155 (5.1%)
Development of medical condition after birth	9/155 (5.8%)
Interruption of pregnancy	6/155 (3.9%)
Late fetal deaths (≥20 weeks)	6/155 (3.9%)

Source: Adapted from STN 125111/904 Amendment 5 The Pregnancy Registry Interim report, Tables 6, 8, and 9
a. In 3 cases the gestational period corresponding to fetal demise was not reported
b. Including 1 missed abortion that needed curettage
c. 11 cases included a medical history which may provide an alternative etiology for spontaneous abortion, 10 cases are confounded by administration of concomitant medications or vaccines, 13 cases in a woman over 30 years of age.

In summary, the pregnancy registry data demonstrated that the most common pregnancy outcome reported after Adacel was administered during pregnancy was delivery of a normal baby. The few cases of congenital anomalies that were reported revealed no anomaly pattern, and the cases observed could not be directly linked to vaccine administration. Although maternal outcomes (e.g., pre-eclampsia, gestational diabetes, gestational hypertension, premature rupture of membranes, and premature labor and delivery) were reported, the background prevalence of these outcomes limit the assessment of the causality with the vaccine. No new safety signals were reported after Adacel vaccine exposure during pregnancy.

In conclusion, the results of the data from the Adacel pregnancy registry are consistent with the Applicant's statement that the evidence currently available supports the safety for both the women vaccinated with Adacel during their pregnancy and their infants. Please see additional details regarding the Adacel Pregnancy registry in the OBPV/DPV reviewer memorandum.

6. INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study Td500059

NCT#05040802
Title: "Effectiveness of Adacel Vaccination in Pregnancy at Preventing Pertussis in Infants <2 Months of Age in the United States (US)"

Study Overview: Study Td500059 was re-analysis of Adacel-related vaccine effectiveness from a Phase 4, observational, individually matched case-control (1:3) study performed by the US CDC originally conducted to determine the effectiveness of Tdap regardless of vaccine brand

against pertussis disease in infants <2 months of age whose mothers were vaccinated with Tdap during pregnancy (Skoff, et al., 2017).

6.1.1 Objectives and Endpoints

Primary Objective

1. To determine the effectiveness of Adacel against pertussis disease in infants <2 months when administered during pregnancy following the current ACIP recommendations, i.e., from 27 to 36 weeks of gestation, and 14 days or more before delivery.
   Endpoint: Pertussis disease in infants younger than 2 months of age.

Secondary Objectives

1. To determine the effectiveness of Adacel against pertussis disease in infants <2 months when administered to:
   a. Pregnant women:
      i. During the third trimester and 14 days or more before delivery
      ii. During the second and third trimesters and 14 days or more before delivery
      iii. During the first and second trimesters and 14 days or more before delivery
      iv. At any point during pregnancy and 14 days or more before delivery
   b. Pre-pregnancy
   c. Postpartum or less than 14 days before delivery

2. To determine the effectiveness of Adacel against hospitalization due to pertussis disease in infants <2 months when administered to:
   a. Pregnant women:
      i. According to the ACIP recommendation of vaccination from 27 through 36 weeks gestation and 14 days or more before delivery
      ii. During the third trimester and 14 days or more before delivery
      iii. During the second and third trimesters and 14 days or more before delivery
      iv. During the first and second trimesters and 14 days or more before delivery
      v. At any point during pregnancy and 14 days or more before delivery
   b. Pre-pregnancy
   c. Postpartum or less than 14 days before delivery

   Endpoint: Pertussis disease requiring hospitalization in infants younger than 2 months of age.

6.1.2 Data Sources

CDC study (Skoff, et al., 2017)
Pertussis cases and controls were identified from data collected at six sites comprising the CDC's Emerging Infection Program Network; study period for the CDC study was from January 1, 2011, to December 31, 2014. The post hoc analysis was completed September 16, 2021.

Infants:

- Were eligible for enrollment if they were at least 2 days old, born in a hospital in their state of residence, at least 37 weeks of gestational age at birth, not adopted or in foster care, and did not live in a residential care facility.

- A pertussis case was defined as a cough illness and at least one of the following: laboratory confirmation (PCR or culture), epidemiological linkage to a laboratory-confirmed pertussis case, or cough lasting two or more weeks with paroxysms, inspiratory whoop, or post-tussive vomiting.
- Infants were included as cases if they met the infant eligibility criteria, were living in the catchment area on their cough onset date and met the pertussis case definition.
- Potential control infants were identified based on birth certificates of infants born at the same hospital as the corresponding case infant, and with the goal of collecting three controls per case. Infants were eligible as controls if they met the infant eligibility criteria, were born at the same hospital as a case infant, were less than two months old on a case infant's cough onset date and did not have a pertussis diagnosis prior to the case infant's cough onset date.
- Information about household size, maternal education, household member with a pertussis diagnosis, and infant's age in weeks were obtained from maternal telephone interviews, medical provider interviews, birth certificate records, and surveillance case report forms.

Maternal Tdap exposure:
Immunization information, including immunization date and vaccine type, manufacturer, brand, and lot, was collected from medical providers or state immunization registries for the mothers of all enrolled infants.

- Mothers were categorized as unvaccinated if they had no evidence of at least one Tdap vaccination given at least two weeks prior to their corresponding case infant's cough onset date. If multiple Tdap doses were identified, the most recent was used to classify the mother's exposure relative to pregnancy.
- Mothers were classified as vaccinated
  - before pregnancy if their most recent Tdap dose was given on or before their pregnancy start date
  - during the 1st or 2nd trimester if their most recent Tdap dose was given after their pregnancy start date and <189 days after their pregnancy start date
  - during the 3rd trimester if their most recent Tdap dose was given at least 189 days after their pregnancy start date and at least 14 days before their infant's date of birth
  - after pregnancy if their most recent Tdap dose was given post-partum or no more than 14 days before their infant's date of birth and at least 14 days before their corresponding case infant's cough onset date.
- Pregnancy start date was calculated from the infant's date of birth and gestational age.

- Trimesters were defined using the CDC definitions in the Skoff, et al. publication:
  - First trimester: 0 to ≤84 days (0 to 11 weeks and 6 days)
  - Second trimester: ≥85 days and ≤188 days (12 weeks to 26 weeks and 6 days)
  - Third trimester: ≥189 days (27 weeks or greater)

Please see CBER statistical review memo for comments about the data source limitations (e.g., data collection, analysis methods).

6.1.3 Statistical Analysis Plan

Sample size
The Skoff, et al. study estimated a vaccine effectiveness for Tdap vaccines of 77.7% (95%CI: 48.3%, 90.4%) when vaccination with any Tdap vaccine took place in the third trimester; the Applicant states that other publications for Adacel and Repevax (Tdap-IPV, Sanofi, UK; a non-

US licensed vaccine) have shown effectiveness greater than 90% with the lower bound of the confidence interval higher than 80% when administered after the 28th gestational week. Considering a potential range in effectiveness (from 65 to 95%, minimum 80% hypothesized), various vaccination rates in the controls, two-sided confidence interval of 95%, low correlation between case and control exposures for the matched pairs, and that finding three controls was not possible for all cases, it was determined that the study would be powered for the primary objective with a number of cases between 40 and 111 (depending on proportions of vaccinated).

Methods

All variables in the study were analyzed descriptively using proportions for categorical variables and mean or median with respective dispersion measurements (standard deviation, first and third quartiles, minimum, and maximum) for continuous variables. The number of missing observations was also assessed.

The distribution of sociodemographic characteristics between the cases and controls was described and compared using univariate conditional logistic regression with respective 95% confidence intervals of the odds ratio (OR).

Other variables were described by cases, controls and overall. No comparison was be performed for:

- Gestational age in days at maternal vaccination
- Hospitalized infants
- Whether the infant have a valid DTaP vaccination before enrollment or not
- Whether the mother receive more than one dose of Tdap or not

There was no imputation of missing data in the analysis.

Vaccine effectiveness (VE) was estimated as VE=(1-OR) x 100% using unadjusted and adjusted odds ratios. The 95% confidence interval of the odds ratio was used to determine the confidence intervals of the VE.

Data management

(b) (4), a Contract Research Organization, was employed for the transfer of the database from the CDC to a Sanofi database as well as to perform the coding and data analysis. The CDC took measures to ensure that on transfer, patient-protected health information was not disclosed.

Changes in the conduct of the study and planned analyses

There were no changes in the conduct of the study.

Reviewer Comment:

Conclusions regarding this VE analysis have some limitations, since the results are based on analyses performed post hoc (i.e., hypotheses not pre-specified) and based on data from a retrospective observational (i.e., non-randomized) study which does not account for unrecognized bias.

6.1.4 Study Population

6.1.4.1 Subject Disposition

The database consisted of 775 infants. Among them, a total of 462 infants were included in the study (160 cases and 302 controls) according to inclusion and exclusion criteria. Common reasons for exclusion included: non-Adacel brand vaccine administered, infants with mothers that could not be reached, mothers that did not consent, incomplete maternal vaccination history follow-up, did not speak English or Spanish, or another reason for non-enrollment. In the original re-analysis, infants <2 weeks of age were additionally excluded. Compared with unenrolled infants with pertussis, mothers of enrolled infants were significantly more likely to have post–high school education; no significant differences were observed for sex, race, ethnicity, hospitalization, outcome, or insurance type.

Among the 160 selected cases 57 (35.6%) had 1 selected control, 64 (40.0%) had 2 selected controls, and 39 (24.4%) had 3 selected controls.

A total of 316 infants were hospitalized with pertussis, 105 were cases and 211 were controls. Among them, 28 (26.7%) had 1 selected control, 48 (45.7%) had 2 selected controls and 29 (27.6%), had 3 selected controls.

Analysis sets

Infants of unvaccinated mothers and mothers vaccinated with Adacel following ACIP recommendations and 14 days or more before delivery
This analysis set included all infants of unvaccinated mothers as well as all infants whose mothers were vaccinated with Adacel following the ACIP recommendations and 14 days or more before delivery. Any case without a control or a control without a matching case was excluded from this analysis set. Seventy-five of the selected cases (46.9%) and 110 of the selected controls (36.4%) were selected for inclusion in this analysis set.

Infants of unvaccinated mothers and mothers vaccinated with Adacel during the third trimester and 14 days or more before delivery
This analysis set included all infants of unvaccinated mothers as well as all infants whose mothers were vaccinated with Adacel following during the third trimester and 14 days or more before delivery. Any case without a control or a control without a matching case was excluded from this analysis set. Seventy-six of the selected cases (47.5%) and 111 of the selected controls (36.8%) were selected for inclusion in this analysis set.

*Ho*spitalized with pertussis
With the same definitions as above used for hospitalized cases, for both analysis sets (infants whose mothers were vaccinated at the timing of ACIP recommendations [27-36 weeks of gestational age] and 14 days or more before delivery as well as during the third trimester and 14 days or more before delivery), 51 (48.6%) cases and 79 (37.4%) controls were selected for inclusion.

Table 5. Subject Disposition, Study Td500059

Population	Cases n (%)	Matched Controls n (%)	Total n (%)
Td500059 re-analysis set	160 (100)	302 (100)	462 (100)
Unvaccinated	92 (57.5)	136 (45.0)	228 (49.4)
Born to mothers vaccinated with Adacel during pregnancy	8 (5.0)	41 (13.6)	49 (10.6)
Vaccinated in the 1st trimester	0	3	3
Vaccinated in the 2nd trimester	2	5	7
Vaccinated in the 3rd trimester	6	33	39
Vaccinated following ACIP recommendations[a]	5	33	38
Vaccinated before pregnancy	14 (8.8)	36 (11.9)	50 (10.8)
Vaccinated after pregnancy	46 (28.8)	89 (29.5)	135 (29.2)

Source: Adapted from STN 125111/904.0 Td500059 CSR, Tables S1, S3, and Skoff (MF5-(b) (4) datasets
Abbreviations: ACIP=Advisory Committee on Immunization Practices; n/%=number/percentage of participants in a given category
a. ACIP currently recommends that all pregnant women be vaccinated with Tdap vaccine between 27-36 weeks of gestation.
Note: The totals from the CDC study included the following: Cases=240, Matched controls=535, Total=775

6.1.4.2 Demographic and Baseline Characteristics

Demographic data is summarized in Table 6.

The median age of infants at the timing of onset of their cough was 5 weeks with a range of 2 weeks to 8 weeks. The majority of infants (34.0%) were between 6 and 7 weeks of age, with 51 (31.9%) of the cases and 106 (35.1%) of the matched controls falling into this age range. Similar to the CDC study population (Skoff, et al., 2017), a majority of the participants were of Hispanic ethnicity (53.9%). Data on ethnicity was missing from 2 participants.

The median age of infants hospitalized with pertussis at the timing of onset of their cough was the same as the entire cohort with overall similar demographics as the entire cohort. Infants of mothers who were vaccinated before pregnancy or not vaccinated at all were found to have a higher likelihood of developing pertussis disease in association with Hispanic ethnicity (OR 3.562, 95% confidence interval [CI]: 1.398, 9.076, p=0.008; OR 2.251, 95% CI: 1.232, 4.114, p=0.008; respectively). No other association between timing of vaccination, demographic characteristic and pertussis disease was identified.

Of the 462 infants included in the study, 16 (3.5%) had another member of their household diagnosed with pertussis. Four infants (0.9%) had a valid DTaP vaccine before enrollment (2 Cases, 2 Controls).

Of the 316 infants hospitalized with pertussis, 10 (3.2%) had another member of their household diagnosed with pertussis. Three infants (0.9%) had received a valid dose of DTaP vaccine before enrollment (2 Cases, 1 Control).

Table 6. Demographic and Baseline Characteristics, Infants 0 to 8 Weeks of Age, by Case Status, Study Td500059

Characteristic	Cases n (%)	Controls n (%)
Total Number of Participants[a]	160	302
Age (Weeks)	--	--
0 – 1[a]	0	0
2 – 3	45 (28.1)	86 (28.5)
4 – 5	43 (26.9)	83 (27.5)
6 – 7	51 (31.9)	106 (35.1)
≥8	21 (13.1)	27 (8.9)
Sex	--	--
Male	78 (48.8)	142 (47.0)
Female	82 (51.3)	160 (53.0)
Race	--	--
White	134 (83.8)	233 (77.2)
Black	14(8.8)	24 (7.9)
Other	10 (6.3)	36 (11.9)
Missing	2 (1.3)	9 (3.0)
Ethnicity	--	--
Hispanic	100 (62.5)	148 (49.0)
Not Hispanic	59 (36.9)	153 (50.7)
Missing	1 (0.6)	1 (0.3)
State of birth	--	--
California	108 (67.5)	205 (67.9)
Connecticut	10 (6.3)	24 (7.9)
Minnesota	12 (7.5)	19 (6.3)
New Mexico	15 (9.4)	28 (9.3)
New York	9 (5.6)	16 (5.3)
Oregon	6 (3.8)	10 (3.3)
Pertussis vaccination[b]	2 (1.3)	2 (0.7)
Mother's education status	--	--
High school or less	95 (59.4)	100 (33.1)
More than high school	65 (40.6)	202 (66.9)
Family size	--	--
Two or fewer	17 (10.6)	79 (26.2)
Three or more	143 (89.4)	223 (73.8)
Pertussis diagnosis at home	--	--
Yes	16 (10.0)	0 (0.0)
No	144 (90.0)	302 (100.0)
Was the infant hospitalized?	--	--
Yes	157 (62.5)	0
No	81 (32.3)	0
Unknown	13 (5.2)	0

Source: Adapted from the Td500059 (BLA 125111/904.0) and Skoff (MF5-(b) (4)) datasets
N=total number of participants. n/%=number/percentage of participants in a given category
Age (weeks)=age expressed in weeks at the date of the onset of cough
a. Study Td500059 excluded infants who had cough onset at <2 weeks of age.
b. Infants exposed to a pertussis-containing vaccine at least 14 days before their enrollment date.

6.1.4.3 Maternal Adacel Exposure

Table 7 presents the timing of vaccination for mothers exposed to Adacel, and mothers unexposed to Adacel (unvaccinated). Seventy-six cases and 111 controls were born to mothers who received Adacel during the third trimester of pregnancy.

Table 7. Timing of Maternal Exposure to Adacel for Infants with Pertussis Disease, Study Td500059

Maternal Vaccination Timing	Cases N=160 n (%)	Controls N=302 n (%)
Before pregnancy	83 (51.9)	126 (41.7)
First or second trimester and 14 days or more before delivery	67 (41.9)	98 (32.5)
Third trimester and 14 days or more before delivery	76 (47.5)	111 (36.8)
Following ACIP recommendations (27-36 weeks of gestational age) and 14 days or more before delivery	75 (46.9)	110 (36.4)
After pregnancy or 14 days or less before delivery	121 (75.6)	207 (68.5)

Source: Adapted from BLA 125111/904.10 Td500059 CSR Table 4.1
Note: Maternal vaccination timing analysis sets were defined based on the different timings of vaccination defined in the protocol and the Statistical Analysis Plan and were not mutually exclusive.

6.1.5 Effectiveness Analyses Results

6.1.5.1 Primary Objective (Original re-analysis excluding infants <2 weeks of age)

In the analysis of vaccination with Adacel following the current ACIP recommendations and 14 days or more before delivery, of the 75 infants who developed pertussis, 3 (4.0%) had been exposed to Adacel in utero, while 72 (96.0%) had not. Among the 110 matched controls, 18 (16.4%) had been exposed to Adacel in utero, while 92 (83.6%) had not. The unadjusted vaccine effectiveness was 91.5% (95% CI: 34.8%, 98.9%). When adjusted for the household size, highest level of maternal education, and infant's age at cough onset, the vaccine effectiveness was 92.5% (95% CI: 38.5%, 99.1%). When adjusted for household size, highest level of maternal education, household member with pertussis diagnosis, and infant's age at cough onset, vaccine effectiveness was 92.4% (95% CI: 38.1%, 99.1%).

6.1.5.2 Secondary Objective (Original re-analysis excluding infants <2 weeks of age)

Secondary endpoint 1:
The vaccine effectiveness for the secondary objective time periods were as follows:

- Pregnant women:
  - During the third trimester and 14 days or more before delivery, unadjusted: 91.5% (95% CI: 34.8, 98.9)
    - Adjusted for the household size, highest level of maternal education, and infant's age: 92.5% (95% CI: 38.6, 99.1)
  - During the second and third trimesters and 14 days or more before delivery, unadjusted: 79.9 (95% CI: 30.1, 94.2)
    - Adjusted for the household size, highest level of maternal education, and infant's age: 82.2% (95% CI: 33.8, 95.2)
  - During the first and second trimesters and 14 days or more before delivery, unadjusted: 47.5 (95% CI: -175.5, 90.0)
    - Adjusted for the household size, highest level of maternal education, and infant's age: 40.5% (95% CI: -241.8, 89.6)

  - At any point during pregnancy and 14 days or more before delivery, unadjusted: 81.1 (95% CI: 34.9, 94.5)
    - Adjusted for the household size, highest level of maternal education, and infant's age: 83.1% (95% CI: 37.9, 95.4)
- Pre-pregnancy, unadjusted: 68.3 (95% CI: 12.4, 88.6)
  - Adjusted for the household size, highest level of maternal education, and infant's age: 74.8% (95% CI: 17.7, 92.3)
- Postpartum or less than 14 days before delivery, unadjusted: 19.0 (95% CI: -39.8, 53.1)
  - Adjusted for the household size, highest level of maternal education, and infant's age: 3.4 (95% CI: -79.5, 48.0)

Secondary endpoint 2:
Vaccine effectiveness could not be calculated for mothers who received vaccination as per ACIP recommendations or for mothers who received vaccination during the third trimester and 14 days before delivery due to low numbers of infants born to mothers vaccinated at the corresponding time periods and low number of matched controls within the conditional logistic regression analysis.

The unadjusted vaccine effectiveness for other maternal vaccination time periods were as follows:
- Pregnant women:
  - During the second and third trimesters and 14 days or more before delivery: 89.0 (95% CI: 11.6, 98.6)
  - During the first and second trimesters and 14 days or more before delivery: 68.1 (95% CI: -190.4, 96.5)
  - At any point during pregnancy and 14 days or more before delivery: 90.1 (95% CI: 21.6, 98.8)
- Pre-pregnancy: 93.7 (95% CI: 51.4, 99.2)
- Postpartum or less than 14 days before delivery: 36.6 (95% CI: -27.0, 68.3)

6.1.5.3. Primary Objective (Re-analysis inclusive of infants <2 weeks of age)

At CBER's request, a re-analysis was performed to include all infants (including those <2 weeks of age) with the primary objective as follows:

1. To determine the effectiveness of Adacel against pertussis disease in infants <2 months when administered during the third trimester of pregnancy and 14 days or more before delivery.

The re-analysis, inclusive of infants <2 weeks of age, led to the inclusion of 5 additional cases and 5 additional controls. The demographic characteristics of the infants included in the post hoc analysis was overall similar to the that of the original analysis set.

Two analyses were performed with cases and controls matched based on:
- selected cases and their birth hospital-matched controls belonging to the same age group at index date (<2 weeks or ≥2 weeks of age).
- selected cases and their birth hospital-matched controls only

*Vaccine effecti*veness of Adacel against pertussis disease when administered in the third trimester of pregnancy when matched based on birth hospital and age (< 2 weeks or ≥ 2 weeks)

In the analysis of vaccination with Adacel during the third trimester and 14 days or more before delivery, of the 81 infants who developed pertussis, 5 (6.2%) had been exposed to Adacel in utero, while 76 (93.8%) had not. Among the 116 matched controls, 19 (16.4%) had been exposed to Adacel in utero, while 97 (83.6%) had not. The unadjusted vaccine effectiveness was 83.1% (95% CI: 24.9%, 96.2%). When adjusted for the household size, highest level of maternal education, and infant's age at cough onset, the vaccine effectiveness was 84.3% (95% CI: 24.8%, 96.7%). When adjusted for household size, highest level of maternal education, household member with pertussis diagnosis, and infant's age at cough onset, vaccine effectiveness was 84.2% (95% CI: 24.5%, 96.7%).

Vaccine effectiveness of Adacel against pertussis disease when administered in the third trimester of pregnancy when matched based on birth hospital only

In the analysis of vaccination with Adacel during the third trimester and 14 days or more before delivery, of the 101 infants who developed pertussis, 5 (5.0%) had been exposed to Adacel in utero, while 96 (95.0%) had not. Among the 171 matched controls, 27 (15.8%) had been exposed to Adacel in utero, while 144 (84.2%) had not. The unadjusted vaccine effectiveness was 87.1% (95% CI: 43.4%, 97.4%). When adjusted for the household size, highest level of maternal education, and infant's age at cough onset, the vaccine effectiveness was 88.0% (95% CI: 43.8%, 97.4%). When adjusted for household size, highest level of maternal education, household member with pertussis diagnosis, and infant's age at cough onset, vaccine effectiveness was 87.3% (95% CI: 39.6%, 97.3%).

It was determined that matching based on birth hospital with adjustments for household size, highest level of maternal education, and infant's age at cough onset provides a more precise estimate of the VE than matching based on birth hospital and age (<2 weeks and ≥2 weeks). Please see the statistical review memorandum for further details on the statistical strategy for the re-analysis.

6.1.5.4 Subpopulation Analyses

Subgroup analyses based on race, sex, and ethnicity of the infant cases and controls were not provided.

6.1.6 Study Summary and Conclusions

Td500059 was the main study to support the effectiveness of Adacel immunization of pregnant individuals during the third trimester to prevent pertussis in infants <2 months of age. In this study, Adacel-relevant data were re-analyzed from an observational case-control study of Tdap VE (Skoff, et al., 2017) in which the VE of Tdap vaccination (not brand specific) in the third trimester was estimated to be 77.7 (95% CI: 48.3, 90.4). The use of this real-world evidence was considered an acceptable regulatory approach to confirming VE since conduct of a randomized, placebo-controlled study evaluating the use of Adacel (US formulation) in pregnant individuals was not feasible due to an existing CDC recommendation for use of Tdap vaccines during each pregnancy.

The observational case-control study reported by Skoff, et al. included cases of pertussis among infants born to mothers vaccinated with Adacel or another Tdap vaccine (Boostrix,

GSK). The re-analyses supporting effectiveness of Adacel are limited to infant cases and controls born to mothers vaccinated with Adacel in the third trimester and 14 days before delivery. Cases of pertussis in infants <2 weeks of age were excluded in the analyses reported by Skoff, et al. but are included in the re-analyses of Adacel effectiveness in preventing pertussis in the first 2 months of life, as described in this review. In the main re-analysis supporting effectiveness of Adacel, 101 infants were identified to have developed pertussis, including 5 (5.0%) who had been exposed to Adacel in utero; among the 171 controls matched on birth hospital, 27 (15.8%) had been exposed to Adacel in utero. Adjusting for infant age, maternal education, and household size, the vaccine effectiveness of Adacel maternal vaccination when administered to mothers during third trimester of pregnancy was estimated as 88.0% (95% CI: 43.8, 97.4).

Interpretations of study Td500059 re-analyses have some notable limitations. The re-analyses were performed post hoc (e.g., hypotheses not pre-specified) based on a dataset from a retrospective observational case-control study. Because participants were not randomized, the results can be affected by unrecognized and uncontrolled bias. Also, there could be more missing or inconsistent data compared to data from a prospective study design. Exclusion of pertussis cases occurring among premature infants (<37 weeks gestation) and exclusion of potential cases when vaccination occurred within 2 weeks prior to delivery may result in estimates of VE that do not reflect more real-world conditions regarding fetal outcomes and vaccination timing of pregnant mothers. Additionally, the high proportion of Hispanic/Latina participants does not represent the demographics of the entire US. Considering these limitations, the estimated vaccine effectiveness from the re-analysis is likely not an exact estimate of the effectiveness of Adacel when used routinely in accordance with the proposed indication. However, acknowledging these limitations, the study has clearly demonstrated a strongly positive vaccine effect in preventing neonatal pertussis when used for maternal immunization.

6.2 Study Td512

NCT# 00258882
Title: “Post-licensure Safety Surveillance Study of Routine Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Adacel)”

Study Overview: Study Td512 was a post-licensure safety surveillance study of the routine use of Adacel. Screening for maternal and fetal outcomes in women exposed to Adacel during pregnancy was performed.

6.2.1 Objectives

Safety Objectives and Endpoints

1. To further characterize the vaccine safety profile and to identify any signals of potentially vaccine-related AEs not detected during pre-licensure studies.

Endpoint: The observational endpoints for the safety evaluation were AEs and SAEs.

6.2.2 Design Overview

This study was a descriptive, epidemiological surveillance study using a large healthcare organization (Kaiser Permanente, KP) to identify any risks or uncommon events associated with the use of Adacel. Medical encounter, emergency room (ER), hospitalization, laboratory, and related databases were reviewed to identify all medical care events at the KP study sites for

vaccinees for the 6-month period following vaccination. State death reports were also reviewed. All ER visits and hospitalizations were included. Outpatient surveillance was limited to:

- Specified neurological conditions (Bell's palsy, seizure, neuritis [included optic neuritis], neuralgia, neuropathy, Guillain-Barré Syndrome, encephalopathy, encephalitis, epilepsy, transverse myelitis, and multiple sclerosis)
- Hypersensitivity reactions (including urticaria, angioedema, and anaphylaxis)
- New-onset autoimmune disease (including idiopathic thrombocytopenic purpura, diabetes, rheumatoid arthritis, hemolytic anemia, lupus, scleroderma, and mixed connective tissue disease). Evaluation of new-onset autoimmune disease was restricted to persons who had been continuously enrolled as plan members for at least 2 years.
- Non-traumatic joint disease (arthritis, arthralgia, or arthropathy)
- Visits for management of pregnancy, childbirth, spontaneous or therapeutic abortion, fetal demise or complications thereof among persons given Adacel vaccine while pregnant
- Febrile illnesses and severe local reactions within 14 days of Adacel receipt, for which medical attention was sought

6.2.3 Population

The investigational group consisted of all individuals who received Adacel vaccine during the study period. The sub-groups included the following:

- Group 1: Persons pregnant at the time of vaccination with Adacel or who became pregnant within 28 days after vaccination.
- Group 2: All other Adacel recipients, classified by age:
  - Subgroup 1, younger than 11 years
  - Subgroup 2, 11 through 17 years
  - Subgroup 3, 18 through 39 years
  - Subgroup 4, 40 through 64 years
  - Subgroup 5, older than 64 years

Vaccinees were assigned to only 1 group according to the following hierarchy: Pregnant vaccinees followed by all other Adacel recipients.

For some analyses, a separate control group was defined for comparison of medical care events; for some, the vaccinee served as her/his own control; and for some, there was no comparison group.

Surveillance included all recipients of Adacel vaccine at the KP study sites to reach a total of 10,000 adolescent (ages 11 to 17 years, inclusive) and 6,000 adult (ages 18 to 64 years, inclusive) vaccinees. There were no selection requirements.

Databases were reviewed to determine:

- Vaccinations administered
- Clinic and ER visit diagnoses
- Inpatient diagnoses, as obtained from International Coding of Diseases (9th Edition) (ICD-9) coding
- Non-Kaiser hospitalizations among Kaiser members
- State Mortality Tapes were reviewed for identification of all deaths.

At the end of the study, line listings of all AEs were provided by KP Vaccine Study Center (KPVSC) that included:

- Subject identification number
- Sex
- Days since injection
- AE visit date
- Age at AE visit date
- Diagnostic category (e.g., ICD-9 decode)
- Relation
- Seriousness

6.2.5 Sites and Centers

KPVSC coordinated collaboration between 3 KP sites: KP Northern California, KP Northwest, and KP Colorado. Vaccination databases were reviewed to identify individuals receiving Adacel.

6.2.6 Surveillance/Monitoring

Surveillance for pregnancy
KP study site databases were reviewed to identify Adacel recipients who were pregnant at the time of vaccination or within 28 days of vaccination. Pregnancies were identified by positive pregnancy tests, prenatal visits within 9 months prior to vaccination with no record of pre-vaccination delivery or abortion, prenatal visits, therapeutic abortions, or deliveries within 10 months after vaccination. Further review (including chart review, provider interview, vaccinee interview, or other steps as may have been appropriate) was conducted to identify those for whom it could not be excluded that the individual was pregnant at the time of vaccination or within 28 days of vaccination. These pregnancies were reported by KPVSC to the Adacel pregnancy registry.

For all pregnancies for which it could not be excluded that the individual was pregnant at the time of vaccination or within 28 days of vaccination, all maternal and fetal (through 1 month of life) outcomes were counted. If there were at least 25 such pregnancies, then for each pregnant individual receiving Adacel vaccine, 3 control individuals not given Adacel vaccine were identified of the same age (±1 year) who had a first positive pregnancy test during the same month (±1 month). Rates of events of maternal and fetal outcomes were compared between the 2 groups.

6.2.7 Statistical Considerations & Statistical Analysis Plan

All data collection was overseen, and analyses were performed by KPVSC.

Sample size
Because this was a retrospective surveillance study performing screening for multiple pre-specified Health Outcomes of Interest and an even larger number of non–pre-specified outcomes with different background incidence rates, no formal calculation of sample size was performed. Surveillance was planned to include all Adacel recipients for 1 year after introduction of Adacel vaccine into KP (September 2, 2005). The protocol specified that if the number of recipients at the 1 year was less than 20,000, surveillance would continue until at least 10,000 adolescent Adacel recipients and 6,000 adult Adacel recipients were under surveillance. At 1-year there were approximately 50,000 adolescent and 70,000 adult members in the study population who received Adacel.

Methods

Group 1

Line listings were prepared detailing all maternal and fetal (through 1 month of age) outcomes. If a nested comparison study was conducted, then rates of maternal and fetal outcomes were determined. Rate ratios were calculated to compare Adacel-exposed and Adacel-unexposed groups, along with 95% CIs.

Group 2

For each age subgroup and relevant time period, and where applicable for each control group, rates of inpatient (defined as involving an overnight stay) hospitalization (excluding elective hospitalizations), of ER visits, and of outpatient visits (as defined in Design Overview) were calculated for all diagnoses combined and by ICD-9, Current Procedural Terminology, or other relevant diagnostic or therapeutic codes. Tables were prepared to present the incidence rates of events under surveillance in the various age groups and time periods. Where applicable, rate ratios were calculated to compare Adacel-exposed and Adacel-unexposed groups or time periods, along with 95% CIs.

All Groups

Should analyses indicate the occurrence of unexpected AEs, or a differential pattern of severe AEs, additional analyses were to be performed as may have been appropriate to further characterize those events or patterns.

Changes to the protocol

Original Protocol: March 17, 2008

Amendment 1 (August 29, 2005) included the following changes:

- Replaced 2 Investigators (Dr. Steve Black and Dr. John Mullooly) with Dr. Roger Baxter and Dr. Sheila Weinmann
- Made other Sanofi and Kaiser personnel changes (including Biostatistician, PSO, CRA)
- Changed center name from Kaiser Permanente Pediatric Vaccine Study Center to Kaiser Permanente Vaccine Study Center
- Removed “monthly line listings” and “cumulative line listings every three months” and retained only “line listing(s).” The large volume of Adacel recipients at the surveillance sites made monthly and cumulative line listings impractical.
- Clarified the control groups
- Deleted the planned interim analysis

Changes in the conduct of the study and planned analyses

Although it was stated in the protocol that analyses were to be conducted separately for the 2 analytical groups (pregnant Adacel recipients and all other Adacel recipients), pregnant Adacel recipients were included in the passive certain surveillance tables and in listings of SAEs that reflected the entire study population.

There were no other changes in the conduct of the study or planned analyses.

6.2.8 Study Population and Disposition

During database surveillance, records of individuals who received Adacel vaccine from September 2, 2005, through October 16, 2006, were searched.

6.2.8.1 Populations Analyzed

All individuals who received Adacel vaccine during the study period were included in the analyses.
Analyses were conducted separately for the 2 analytical groups:

- Individuals pregnant at the time of vaccination with Adacel vaccine or who became pregnant within 28 days after vaccination
- All other Adacel recipients (classified in section 6.2.3)

6.2.8.1.1 Demographics

Overall, 124,139 Adacel recipients were identified during passive surveillance (46% male and 54% female). Of the 64,067 female recipients, 225 were identified as pregnant individuals who had received Adacel during pregnancy or within 28 days before LMP. Controls were identified through passive surveillance including age, sex, race, time/season of vaccination. For each pregnant individual 3 controls were selected from the non-Adacel exposed pregnant women, with 675 women identified this way. These controls may or may not have received another vaccine. The total amount of participants (recipients and controls) enrolled in the study was 900.

The mean age of pregnant women vaccinated with Adacel during the surveillance period was 28.4 years (range 14 years through 51 years). Forty-four percent were White, 11.1% were Asian, 8.4% were Black, and 18.2% were Hispanic/Latino. The demographic characteristics of the control group was similar to the study cohort. Thirty-nine individuals received Adacel within 2 weeks prior to the date of the LMP, 110 were vaccinated during the 1st trimester and 47 were vaccinated during the 2nd or 3rd trimester. For 29 women, the trimester of pregnancy could not be determined. The pregnancy outcomes included 165 live births, 21 spo**ntaneous abortions, 1 late fetal death, 33 elective abortions, 1 ectopic pregnancy, and 4 lost to follow-up.**

Table 8. Demographics and Baseline Characteristics, Study Td512

Characteristic	**Adacel N=225 Value or n (%)**	**Non-Adacel Control N=675 Value or n (%)**
Age (Years)	--	--
<18	18 (8.0)	60 (8.9)
18 to <25	43 (19.1)	132 (19.6)
25 to <35	120 (53.3)	361 (53.5)
35 to <45	41 (18.2)	113 (16.7)
≥45	3 (1.3)	9 (1.3)
Mean	28.4	28.2
Median	28.0	28.0
Minimum	14	14
Maximum	51	52
Race	--	--
Asian	25 (11.1)	77 (11.4)
Black/African American	19 (8.4)	51 (7.6)
Native American[a]	0 (0.0)	3 (0.4)
Pacific Islander	0 (0.0)	2 (0.3)
Multiracial	9 (4.0)	8 (1.2)
White	99 (44.0)	260 (38.5)
Other/Unknown	32 (14.2)	127 (18.8)
Ethnicity	--	--
Hispanic	41 (18.2)	147 (21.8)

Characteristic	Adacel N=225 Value or n (%)	Non-Adacel Control N=675 Value or n (%)
Timing of maternal Adacel vaccination, n (%)	--	--
Prior to pregnancy	39 (17.3)	n/a
<12 weeks gestation	110 (48.9)	n/a
12 to <27 weeks gestation	33 (14.7)	n/a
27 to <36 weeks gestation	11 (4.9)	n/a
≥36 gestation	3 (1.3)	n/a
Post-partum	0 (0.0)	n/a
Unable to estimate[b]	29 (12.9)	n/a
Gestational age at delivery, weeks[c]	--	--
Mean	39	39
Median	39	39

Source: Adapted from STN 125111/904 Td512 CSR Tables 4.5 and 9.7.
Abbreviations: N=number of participants, n=number of participants in a given category, Value=value of the considered parameter, %=n/Number of participants with available results.
a. Although the term used by the Applicant to solicit demographic information was "Native American" this term indicates that the population included individuals who identified as American Indian or Alaskan Native
b. Unable to estimate as LMP is unavailable (live birth=9, spontaneous abortion=7, therapeutic abortion=12, lost to follow-up=1) Restricted to people with live births and known LMP and delivery date
Note: In this table, Adacel group=Mothers received Adacel during pregnancy, control group=Mothers who did not receive Adacel during pregnancy.

6.2.9 Safety Results

6.2.9.1 Pregnancy Outcomes

For the 7 maternal outcomes identified (including live birth, spontaneous abortion, early fetal death, late fetal death, elective abortion, ectopic pregnancy, and lost to follow-up), the rates reported in Adacel exposed women were similar to those in controls (Table 9). The rate of live births was slightly higher among Adacel-exposed women (RR=1.12; 95% CI: 1.02,1.23), and the rate of spontaneous abortions (<20 weeks gestation) was slightly lower in Adacel-exposed women (RR=0.62; 95% CI: 0.40, 0.96).

Table 9. Rate and Relative Risk of Maternal Outcomes in Adacel Recipients

Outcome	Adacel Recipients N=225 n (%)	Non-Adacel Recipients N=675 n (%)	RR (95% CI)	p-value
Live birth	165 (73.3)	442 (65.5)	1.120 (1.017, 1.233)	0.033
Spontaneous abortion (<20 weeks)	21 (9.3)	102 (15.1)	0.618 (0.396, 0.964)	0.033
Early fetal death (>20-27 weeks)	0 (0.0)	1 (0.1)	--	1.000
Late fetal death (≥28 weeks)	1 (0.4)	0 (0.0)	--	0.250
Elective abortion	33 (14.7)	105 (15.6)	0.943 (0.657, 1.353)	0.831
Ectopic pregnancy	1 (0.4)	5 (0.7)	0.600 (0.070, 5.108)	1.000
Lost to follow-up	4 (1.8)	20 (3.0)	0.600 (0.207, 1.737)	0.474

Source: Adapted from 125111/904 study Td512 CSR, Table 5.10
Abbreviations: N=number of participants in study group. n (%) = number (percentage) of participants reporting a specific pregnancy outcome.
Note: In this table, Adacel group=Mothers received Adacel during pregnancy, control group=Mothers who did not receive Adacel during pregnancy.

The rates of 27 unique fetal outcomes were comparable across study groups (Table 10). Three cases of SAE with fatal outcomes were detected in the study and were reported to regulatory authorities. One case involved a pregnant woman (Subject (b) (6) who received a dose of

Adacel vaccine at 2.5 weeks gestation. Complete atrioventricular canal defect was detected in the fetus via ultrasound at 23 weeks gestation. Fetal demise occurred at 33 weeks gestation (200 days post-vaccination). Several dysmorphic features were suggestive of Downs Syndrome, which was confirmed by karyotyping. This event was not considered related to study vaccine. In each of the 2 other cases (Subject (b) (6) and Subject (b) (6), on further follow-up it was determined that the mothers were administered Adacel vaccine more than 30 days before the date of conception. Therefore, the fetus was not considered to be exposed to the vaccine.

Table 10. Rate and Relative Risk of Infant Outcomes in Adacel Recipients

Outcome	Adacel recipients N=225 n (%)	Non-Adacel recipients N=675 n (%)	RR (95% CI)	p-value
Encephalocele	1 (0.4)	0 (0)	-	0.250
Specified congenital anomalies of lacrimal passages	4 (1.8)	18 (2.7)	0.667 (0.228, 1.949)	0.620
Ventricular septal defect	1 (0.4)	2 (0.3)	1.500 (0.137, 16.464)	1.000
Stenosis of pulmonary valve, congenital	0 (0)	1 (0.1)	-	1.000
Patent ductus arteriosus	2 (0.9)	6 (0.9)	1.000 (0.203, 4.919)	1.000
Agenesis, hypoplasia, and dysplasia of lung	0 (0)	1 (0.1)	-	1.000
Cleft palate, unilateral, incomplete	0 (0)	1 (0.1)	-	1.000
Cleft palate with cleft lip, unspecified	0 (0)	1 (0.1)	-	1.000
Tongue tie	1 (0.4)	6 (0.9)	0.500 (0.061, 4.131)	0.687
Undescended testis	0 (0)	1 (0.1)	-	1.000
Hypospadias	2 (0.9)	0 (0)	-	0.062
Congenital chordee	0 (0)	2 (0.3)	-	1.000
Other penile anomalies	0 (0)	2 (0.3)	-	1.000
Other obstructive defects of renal pelvis and ureter	1 (0.4)	0 (0)	-	0.250
Metatarsus varus	1 (0.4)	0 (0)	-	0.250
Polydactyly of fingers	0 (0)	1 (0.1)	-	1.000
Polydactyly of toes	0 (0)	1 (0.1)	-	1.000
Other congenital deformity of hip (joint)	0 (0)	1 (0.1)	-	1.000
Vascular hamartomas	1 (0.4)	2 (0.3)	1.500 (0.137, 5.108)	1.000
Congenital pigmentary anomalies of skin	1 (0.4)	5 (0.7)	0.600 (0.070, 5.108)	1.000
Other specified anomalies of skin	0 (0)	2 (0.3)	-	1.000
Specified congenital anomalies of breast	0 (0)	1 (0.1)	-	1.000
Down's syndrome	0 (0)	1 (0.1)	-	1.000
Congenital anomaly, unspecified	0 (0)	2 (0.3)	-	1.000
Poor fetal growth	5 (2.2)	12 (1.8)	1.250 (0.445, 3.509)	0.777
Excessive fetal growth	4 (1.8)	3 (0.4)	4.000 (0.902, 17.736)	0.070
Unspecified fetal and placental problem	0 (0)	2 (0.3)	-	1.000

Source: Adapted from BLA 125111/904 Study Td512 CSR Table 5.11.
Abbreviations: CI=confidence interval; N=Number of total participants in group; n=number of participants with the listed outcome; RR=relative risk.
Note: In this table, Adacel group=Mothers received Adacel during pregnancy, control group=Mothers who did not receive Adacel during pregnancy.

6.2.9.2 Deaths

There were no deaths recorded among the 225 women who either received Adacel during pregnancy or became pregnant within 28 days after Adacel vaccination.

6.2.10 Study Summary and Conclusions

Study Td512 was a post-licensure safety surveillance study of the routine use of Adacel in which screening for maternal and fetal outcomes in women exposed to Adacel during pregnancy was performed. A total of 225 women between 14 and 51 years of age who received Adacel within 28 days of pregnancy were matched with 675 controls by age and date of pregnancy. There were no identified maternal or fetal outcomes that occurred at rates higher in the Adacel exposed group compared to the control group. The study did not reveal any new safety concerns regarding the use of Adacel during pregnancy. This data supports the safety of the use of Adacel in the third trimester of pregnancy to provide protection against pertussis disease in infants less than 2 months of age. Please see the OBPV/DPV reviewer memorandum for the complete review of this study.

7. INTEGRATED OVERVIEW OF EFFICACY

An integrated summary of efficacy is not presented in this memorandum because data supporting effectiveness for the proposed indication was based on the single study Td500059.

Additional evidence of vaccine effectiveness was provided in the Applicant's Systematic Literature Review submitted as additional information (Section 5.5.2). The summary of these studies and reported results supporting effectiveness of Adacel can be found in the CBER RWE reviewer memorandum.

Taken altogether, results from study Td500059, acknowledging its limitations, along with results from the additional published observational studies, support the effectiveness of Adacel for use during pregnancy to protect the infant against pertussis during the first 2 months of life.

8. INTEGRATED OVERVIEW OF SAFETY

An integrated summary of safety is not presented in this memo because study Td512 was the only study that described pregnancy and neonatal outcomes.

9. ADDITIONAL CLINICAL ISSUES

9.1 Specific Populations

9.1.1 Human Pregnancy Data

Please see clinical review of study Td512 (section 6.2 of this memo).

9.1.2 Use During Lactation

No data are available to assess the effect of administration of Adacel on breastfed infants or on milk production/excretion.

9.1.3 Pediatric Use and PREA Considerations

Adacel is not approved for individuals less than 10 years of age. Safety and effectiveness of Adacel in persons less than 10 years of age in the US have not been established.

This supplement was affected by PREA because a new indication is being requested for the product.

- A partial waiver for studies in pregnant individuals <10 years of age was granted because the vaccine does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group.

- The pediatric study requirement for pregnant individuals 10 through 17 years of age was fulfilled via extrapolation of safety and effectiveness of Adacel in pregnant individuals 14 to 51 years of age because the course of pertussis disease in the offspring, immune responses to vaccination, and transplacental transfer of pertussis maternal antibodies is expected to be similar in pregnant adolescents as compared to pregnant adults. Adacel is approved for active booster immunization in individuals 10 through 64 years of age to prevent pertussis, tetanus, and diphtheria.

9.1.4 Immunocompromised Patients

No data available.

10. CONCLUSIONS

The safety and effectiveness data in this sBLA support revisions to the Adacel prescribing information for the proposed indication and use.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 11. Risk-Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Pertussis disease, caused by the bacterium *Bordetella pertussis*, is a respiratory illness affecting all age groups. The morbidity associated with pertussis is highest in infants <6 months of age; in 2021, the highest incidence of reported pertussis cases in the US was in infants <6 months of age. The case-fatality rate for pertussis among infants younger than six months of age was approximately 1%, with the majority of deaths occurring in those younger than two months of age. The most common complications of pertussis infection in infants include apnea, pneumonia, and weight loss secondary to feeding difficulties and post-tussive vomiting. Other complications include seizures and encephalopathy.	Pertussis in infants is a serious medical condition and can be associated with severe complications and long- term sequelae.
Unmet Medical Need	Management of infant pertussis infection includes antimicrobial therapy and supportive care. Preventive measures include age-appropriate immunization against pertussis for infants starting as early as 6 weeks of age, children, adolescents, adults, and unimmunized/partially immunized close contacts of the index case.	Primary active immunization of infants against pertussis consists of a multiple dose series, beginning as early as 6 weeks of age. There is an unmet medical need for effective prevention in infants, especially in infants younger than 2 months of age.
Clinical Benefit	The effectiveness of Adacel immunization during the third trimester of pregnancy to prevent pertussis among infants <2 months of age was based on a re-analysis of Adacel data (study Td500059) from an observational case- control study of Tdap vaccine effectiveness (VE). The Td500059 re-analyses were performed post hoc and based on data from a retrospective observational study (Skoff, et al., 2017).	Immunization during pregnancy can provide passive protection against pertussis in infants younger than 2 months of age. Overall, results of the re-analyses of Adacel data from the case-control study (Skoff, et al., 2017) demonstrated that Adacel was statistically likely to be effective for the intended indication, and the results were robust to the analysis methods and missing data.
Risk	The safety of Adacel administered to women during the third trimester of pregnancy was evaluated in study Td512, a post-licensure safety surveillance study. No vaccine-related adverse effect on pregnancy or the fetus/newborn child were identified. An increased risk (RR<1.25) of chorioamnionitis was identified in a Vaccine Safety Datalink study, though no vaccine-related adverse effects on the infants were identified.	The observational data provided in the license application supplement support the safety of Adacel when administered during the third trimester of pregnancy for both vaccinated mothers and infants.

Risk Management	Since CDC's recommendation in 2012, there has been widespread use of Tdap vaccines during pregnancy. Review of pregnancy registry data suggested there was no risk to the mother, the fetus, or the infant from routine vaccination in the third trimester of pregnancy. Interpretation of potential risks associated with vaccination during pregnancy in this registry was limited because observational data were mainly reported retrospectively.	The Applicant agreed to conduct an observational safety cohort study using electronic health care data with linkage to offspring and access to clinical records in the US, to evaluate pregnancy outcomes in individuals exposed to Adacel as a post- marketing commitment (PMC). The study will include pre-defined pregnancy, birth and neonatal outcomes, including chorioamnionitis and premature birth. From the clinical reviewer's perspective this an adequate measure to further evaluate the risk of Adacel when administered during pregnancy.

11.2 Risk-Benefit Summary and Assessment

Prevention of pertussis in infants younger than 2 months of age could potentially prevent severe complications and long-term sequelae associate with pertussis disease. The benefit of Adacel immunization during the third trimester of pregnancy to prevent pertussis in infants <2 months of age was supported by results from a re-analysis of Adacel data (study Td500059) from a retrospective case-control study.

The safety of Adacel immunization during pregnancy was supported by a post-licensure surveillance study (Td512) in which no vaccine-related adverse effect on pregnancy or the fetus/newborn child were identified.

Additional data to support the safety of Adacel administered during pregnancy, includes the Adacel pregnancy registry which most often reported delivery of a normal baby after Adacel exposure during pregnancy and no anomaly pattern or direct link of anomaly cases to vaccine administration.

A Systematic Literature Review of provided data from 18 studies, including the review of 4 randomized clinical trials, that summarized the current data available for the safety of Adacel exposure during pregnancy and demonstrated that the known and potential risks include common local and systemic adverse reactions (e.g., pain/redness/swelling at the injection site). No conclusive association of any adverse outcome with Adacel vaccination during pregnancy was found for the mother or infant in these studies.

In conclusion, pertussis in infants is a serious, and sometimes fatal, medical condition that can lead to severe complications and long-term sequelae, especially in infants younger than 2 months of age. The benefit of Adacel administered to individuals during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age outweighs the potential risks and uncertainties about decrease effectiveness due to diminished pertussis antibody responses in these infants following primary vaccination series and after a booster dose with DTaP-containing vaccines.

11.4 Recommendations on Regulatory Actions

Based on review of the safety and effectiveness data in this sBLA and the risk-benefit considerations described in section 11, this reviewer recommends approval of Adacel for immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age.

11.5 Labeling Review and Recommendations

The prescribing information was reviewed and specific comments were provided by CBER to the Applicant who made the requested revisions. All issues were satisfactorily resolved.

11.6 Recommendations on Postmarketing Action

The Applicant agreed to a Post-Marketing Commitment to conduct an observational safety cohort study using electronic health care data with linkage to offspring and access to clinical records in the US, to evaluate pregnancy outcomes in individuals exposed to Adacel. The population will be comprised of eligible pregnant individuals exposed to Adacel as of the 1st day of the 27th week of gestation or later and an active comparator of pregnant individuals not vaccinated with any Tdap vaccines during pregnancy. The study will include pre-defined pregnancy, birth and neonatal outcomes.