

## Summary Basis for Regulatory Action

**Date:** January 11, 2019

**From:** Taruna Khurana PhD., Chair of the Review Committee

**BLA STN#:** 125111/679

**Applicant Name:** Sanofi Pasteur Limited

**Date of Submission:** December 12, 2017

**Goal Date:** January 11, 2019

**Proprietary Name/Established name:** Adacel® (Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine Adsorbed, Tdap)

**Indication:** For active booster immunization for prevention of tetanus, diphtheria and pertussis in adolescents and adults 10 through 64 years of age

**Recommended Action:** The Review Committee recommends approval.

**Review Office Signatory Authority:** Doran Fink MD, PhD, Deputy Director, Clinical, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review

- I concur with the summary review.**
- I concur with the summary review and include a separate review to add further analysis.**
- I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

Document title	Reviewer name, Document date
CMC Review(s) <ul style="list-style-type: none"> <li>• <i>CMC (product office)</i> <i>Serology Assays (Diphtheria and Tetanus)</i> <i>Serology Assay (Pertussis)</i></li> <li>• <i>Categorical Exclusion (OCBQ/DMPQ)</i></li> </ul>	Christopher Mocca, July 17, 2018 Rebecca Brady, July 20, 2018  Bradley Dworak, July 26, 2018

<p>Clinical Review(s)</p> <ul style="list-style-type: none"> <li>• <i>Clinical (product office)</i></li> <li>• <i>Postmarketing safety epidemiology review (OBE/DE)</i></li> <li>• <i>BIMO</i></li> </ul>	<p>Ann T. Schwartz January 10, 2019 Patricia Rohan, January 07, 2019</p> <p>Colonious King, September 10, 2018</p>
<p>Statistical Review(s)</p> <ul style="list-style-type: none"> <li>• <i>Clinical data</i></li> <li>• <i>Non-clinical data</i></li> </ul>	<p>YinKiu (Charles) Cheung, January 07, 2019 YinKiu (Charles) Cheung, September 17, 2018</p>
<p>Pharmacology/Toxicology Review</p> <ul style="list-style-type: none"> <li>• <i>Toxicology (product office)</i></li> <li>• <i>Developmental toxicology (product office)</i></li> <li>• <i>Animal pharmacology</i></li> </ul>	<p>Andrew O'Carroll, August 22, 2018</p>
<p>Labeling Review</p> <ul style="list-style-type: none"> <li>• <i>APLB (OCBQ/APLB)</i></li> </ul>	<p>Sonny Saini, August 14, 2018</p>

## 1. Introduction

Adacel (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed [Tdap]) is currently approved as a single booster dose for active immunization against tetanus, diphtheria, and pertussis in adolescents and adults 10 through 64 years of age. The vaccine is manufactured by Sanofi Pasteur Ltd. (Toronto, Canada) and distributed by Sanofi Pasteur, Inc. (Swiftwater, PA). Adacel is available as a suspension for intramuscular injection in 0.5 mL single-dose vials and prefilled syringes.

This supplement for Adacel, submitted on December 12, 2017, included safety and immunogenicity data from clinical studies intended to support removal of the single-dose usage from the currently approved prescribing information, to introduce a proposed dose-interval for administration of a second booster dose of Adacel in adults, and to clarify instructions for usage of Adacel as part of management of tetanus-prone wounds.

Tetanus is caused by *Clostridium tetani* when the bacterial spores enter the body through a breach in the skin and produce tetanus toxin. Tetanus is uncommon in the US, with an average of 30 reported cases each year, with most of these as unvaccinated cases. The infection affects brain and nervous system resulting in severe muscular spasms. The disease has been controlled primarily due to routine immunization practices.

Diphtheria is an acute toxin mediated respiratory disease caused by infection with *Corynebacterium diphtheriae*. Diphtheria is also a rare disease in the US, with two cases reported between 2004 and 2015. The infection is characterized by formation of a pseudomembrane in the upper respiratory tract, potentially extending as far as the tracheobronchial tree.

Pertussis is a respiratory disease caused by *Bordetella pertussis*. The disease is characterized by a prolonged paroxysmal cough. Pertussis is a common disease in the US with frequent outbreaks. According to the CDC's Provisional Pertussis Surveillance Report, over 15,000 pertussis cases were reported in 2017. Since introduction of whole cell pertussis vaccine in the 1940s, the incidence rates have significantly dropped. However, the incidence rate gradually

began to increase with 48,277 cases in 2012. Due to safety concerns the whole cell pertussis vaccines are no longer available in the US. Pertussis antigens are included in combination with tetanus and diphtheria antigens in various acellular vaccines indicated for use in infants and young children (DTaP) and for use in older children, adolescents, and adults (Tdap).

## 2. Background

Adacel is currently indicated for active booster immunization against tetanus, diphtheria, and pertussis in adolescents and adults 10 through 64 years of age.

Adacel was initially approved in the US in 2005 for use as a single-dose booster in persons 11 through 64 years of age. Approval was based on the demonstration of immunologic non-inferiority to a US-licensed tetanus and reduced diphtheria vaccine (Td) and a bridging study showing immunologic non-inferiority of the pertussis antibody responses when compared to the antibody responses associated with protection from pertussis in the Sweden I infant efficacy study. In the Sweden I efficacy study, three doses of DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed / DTaP) demonstrated 85% efficacy against pertussis disease as defined by the World Health Organization (WHO). Adacel and DAPTACEL contain the same pertussis antigens: Pertussis toxoid (PT), Filamentous hemagglutinin (FHA), pertactin (PRN) and fimbriae types 2 &3 (FIM), but in differing amounts as indicated in Table 1 below.

**Table 1: Formulation of Adacel and DAPTACEL Vaccines (0.5 mL dose)**

<b>Components</b>	<b>Adacel (Tdap)</b>	<b>DAPTACEL (DTaP)</b>
Tetanus toxoid	5 Lf	5 Lf
Diphtheria toxoid	2 Lf	15 Lf
Detoxified pertussis toxin	2.5 mcg	10 mcg
Filamentous hemagglutinin	5 mcg	5 mcg
Pertactin	3 mcg	3 mcg
Fimbriae	5 mcg	5 mcg
Aluminum Phosphate (adjuvant)	1.5 mg	1.5 mg

In May 2013, the applicant submitted the results from Study Td519 evaluating safety and immunogenicity of Adacel when administered to subjects 10 to <11 years of age compared with subjects 11 to <12 years of age. Data from Study Td519 supported the approval of the lower age limit of 10 years for vaccination with Adacel.

On June 28, 2017, the applicant submitted a Type C Meeting request under IND 9226 to discuss the safety and immunogenicity data from Study Td537 entitled, "Safety and Immunogenicity in Adults of Revaccination with Adacel Vaccine 10 Years after a Previous Dose." Study Td537 was a Phase 4, randomized, active-controlled study conducted to assess the safety and immunogenicity of a second dose of Adacel when administered to healthy adults  $\geq 18$  to  $\leq 65$  years of age approximately 10 years after the first dose of Adacel. The Type C meeting (CRMTS #10830) was held with the applicant on September 19, 2017, to provide feedback on the acceptability of the data from clinical trial Td537. During the Type C meeting the applicant sought agreement that the data were sufficient to support the removal of the "single-dose" use statement currently in the US prescribing information and would support repeat vaccination with Adacel. During the meeting the recommended interval for re-administration was discussed

with the applicant. CBER suggested that the applicant include safety and immunogenicity data supporting re-administration of Adacel and advised that the interval for Adacel re-administration would be discussed during review of the supplement.

On December 12, 2017, this efficacy supplement for Adacel was submitted under STN 125111/679 which included data from three studies Td537, Td518 and Td506LT to support removal of “single-dose” indication from currently approved prescribing information and introduce a dose-interval for administration of a second dose of Adacel in adults. In the submission the applicant did not propose a re-vaccination interval. However, during the review cycle revisions were made to the prescribing information to address the dose interval and use for tetanus prophylaxis and wound management.

The submission also included data from two supportive trials: the open label safety study, Td518, conducted in healthy adolescents and adults 15 through 69 years of age who received a second dose of Adacel 4-5 years following an initial dose of Adacel; and the long-term antibody persistence study, Td 506LT, which followed subjects 11-64 years of age enrolled in Study Td506 after an initial vaccination with Adacel.

### **3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)**

#### **a) Product Quality**

Each 0.5 mL dose of Adacel contains 5 Lf units tetanus toxoid, 2 Lf diphtheria toxoid, acellular pertussis antigens (2.5 mcg detoxified pertussis toxin, 5 mcg filamentous hemagglutinin, 3 mcg pertactin, 5 mcg fimbriae types 2 and 3) and 1.5 mg aluminum phosphate as adjuvant. As there is no change in the formulation and manufacturing process, the applicant did not submit information on chemistry, manufacturing and controls under this supplement. The formulation of Adacel used in the primary study Td537 is identical to the formulation described in and approved with the original Adacel Biologics License Application (BLA; STN 125111).

#### **b) CBER Lot Release**

The product is under CBER lot release.

#### **c) Facilities review/inspection**

No manufacturing or facilities- and equipment-related information/data was provided in the supplement.

#### **d) Environmental Assessment**

The supplement included a request for a categorical exclusion from an environmental assessment under 21 CFR §25.31 (c). The FDA concluded that this request is justified as the manufacture of Adacel will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment (21 CFR §25.15 (d)).

#### **e) Product Comparability**

N/A

### **4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

No new non-clinical pharmacology/toxicology data was submitted as a part of this supplement. The toxicology reviewer reviewed the relevant language added to the label to comply with the

Pregnancy and Lactation Labeling Rule (PLLR) and determined it to be acceptable. The toxicology studies (Study 407/147; Development Toxicity Study in Rabbit by IM Route and Study C005772; Pre- and Post- Natal Development Toxicity Study) as referenced in the package insert were reviewed as a part of the original BLA approved in 2005.

## **5. CLINICAL PHARMACOLOGY**

No new clinical pharmacology data were submitted as a part of this supplement.

## **6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE**

### **a) Clinical Program**

#### **Primary Study Td537**

Study Td537 was a Phase 4, randomized, observer-blinded, active-controlled, multi-center study. The study was conducted in the US and Canada to assess the safety and immunogenicity of a second injection of Adacel when administered to subjects 8-12 years after the first injection. Healthy adult subjects  $\geq 18$  to  $\leq 65$  years of age previously injected with Adacel were recruited from the primary licensure study, Td506 and, and from the Canadian general public. The subjects were randomized into two groups: group 1 subjects (n=1002 enrolled; 999 planned) received a second vaccination of Adacel, and group 2 subjects (n= 333 enrolled; 328 planned) received Td Adsorbed vaccine (TENIVAC) as an active control. The study population consisted of 858 (64.6%) females and 472 (35.4%) males and this composition was balanced across groups. The mean age was 28.9 years for the Adacel group and 29.2 years for the Td Adsorbed group. At visit one, a single dose of 0.5 mL Adacel or Td Adsorbed vaccine was administered via intramuscular (IM) route. Blood samples were collected at visit 1 (baseline pre-vaccination) and visit 2 (28 days post-vaccination). Safety data were collected for up to 6 months following vaccination from all participants planned for both groups.

The primary immunogenicity objectives of the study were:

- To demonstrate that tetanus and diphtheria seroprotection rates and booster response rates following Adacel were non-inferior to those following Td Adsorbed vaccine;
- To demonstrate that Anti-pertussis antibody geometric mean concentrations (GMCs) elicited by Adacel were non-inferior to those elicited by DAPTACEL vaccine given to infants in historical studies (Sweden I efficacy trial and M5A10), and;
- To demonstrate that Pertussis booster response rates induced by Adacel were non-inferior to expected values.

The following success criteria were applied to establish immunologic noninferiority between Adacel and Td Adsorbed vaccine:

#### **Tetanus and Diphtheria:**

- Seroprotection rates for Adacel were predefined as noninferior to Td Adsorbed vaccine if the lower limit (LL) of the 95% CI for seroprotection rate difference (Adacel minus Td Adsorbed vaccine) was  $> -10\%$  for both

tetanus and diphtheria. Seroprotection was defined as an antibody concentration of  $\geq 0.1$  IU/mL.

- Booster response rates for Adacel were predefined as non-inferior to Td Adsorbed vaccine if the LL of the 95%CI for booster response rate difference (Adacel minus Td Adsorbed vaccine) was  $> -10\%$  for both tetanus and diphtheria. A booster response was defined as at least a 4-fold increase in pre- to post-vaccination antibody concentrations for subjects with a pre-vaccination concentration  $\leq 2.56$  IU/mL for diphtheria and  $\leq 2.7$  IU/mL for tetanus, and as at least a 2-fold increase for subjects with a pre-vaccination concentration  $> 2.56$  IU/mL for diphtheria and  $> 2.7$  IU/mL for tetanus.

#### Pertussis:

- GMCs for Adacel were predefined as immunologically non-inferior to historical controls if the LL of the 2-sided 95% CI of the GMC ratio (Adacel divided by the selected historical control group) was  $> 0.66$  for each antigen (PT, FHA, FIM, and PRN).
- Booster response rates for Adacel were predefined as non-inferior to historical controls if the LL of the 2-sided 95% CI (Adacel divided by the selected control group) was  $> -10\%$  for each antigen. A booster response was defined as at least a 4-fold increase in pre- to post-vaccination antibody concentrations for subjects with pre-vaccination concentrations  $\leq 93$  EU/mL for PT,  $\leq 170$  EU/mL for FHA,  $\leq 115$  EU/mL for PRN, and  $\leq 285$  EU/mL for FIM, and defined as at least a 2-fold increase for subjects with a pre-vaccination concentration  $> 93$  EU/mL for PT,  $> 170$  EU/mL for FHA,  $> 115$  EU/mL for PRN, and  $> 285$  EU/mL for FIM.

#### Clinical Serology Assays:

The response to the diphtheria and tetanus components was measured by a Toxin Neutralization Assay (TNA) and an IgG Enzyme Linked Immunosorbent Assay (ELISA) respectively. The TNA was validated for specificity, accuracy, precision, linearity, and Lower Limit of Quantitation (LLOQ). The tetanus IgG ELISA was validated for precision, linearity, Limit of Detection (LOD) and LLOQ. The antibodies against pertussis antigens (PT, FHA, PRN, and FIM) were measured using an ELISA. The pertussis ELISA assay was validated for specificity, accuracy, repeatability, intermediate precision, linearity, stability, and LLOQ. The validation and assay stability data support the use of these assays for the serology assessment of the study Td537. All assays were validated and performed by Global Clinical Immunology (GCI) at Sanofi Pasteur, Swiftwater.

#### Immunogenicity Analyses:

The Per Protocol analysis set was used for the immunogenicity analyses and included subjects who had received the vaccine, had at least one valid post-vaccination serology result, and had no protocol deviation. The Per Protocol analysis set was comprised of 948 (94.6%) subjects in the Adacel group and 317 (96.6%) subjects in the Td Adsorbed group. Adacel met the prespecified non-inferiority criteria for seroprotection rate differences when compared to Td Adsorbed for both tetanus (0.0% [95%CI -0.4, 1.2]) and diphtheria (0.42% [95%CI -0.3, 2.1]). For tetanus, Adacel did not meet the prespecified non-inferiority criterion for the booster response rate difference compared to the Td

Adsorbed group (-7.12% [95%CI -12.0, -1.7]) because the LL of the 95%CI was < -10%. However, all subjects were already seroprotected against tetanus before the booster dose (GMC 1.18 IU/mL [95%CI 1.10, 1.27]) and overall demonstrated a substantial response to the booster dose (10.1 IU/mL [95%CI 9.59, 10.6]), so this was not thought to be clinically meaningful. For diphtheria, Adacel met the prespecified noninferiority criterion for the booster response rate difference compared to the Td Adsorbed group (-0.95 [95%CI -5.4, 4.0]). The percentage of subjects who gained seroprotection against diphtheria following a second vaccination (99.8% [95%CI 99.2, 100]) was deemed adequate to support re-vaccination.

For pertussis, Adacel was evaluated for non-inferiority in comparison to historical controls for the pertussis antigens contained in the vaccine (PT, FHA, PRN, and FIM), by GMC ratios and booster response rate differences. The control for PT was the group of subjects in US study M5A10, who received 4 doses of DAPTACEL. The control for FHA, PRN, and FIM was the group of subjects from the Sweden I efficacy study who received 3 doses of DAPTACEL. This difference in the control populations was necessitated by concerns about the assay used to measure responses to the PT antigen in the Sweden I study.

Adacel met noninferiority criteria (LL of 95% CI of GMC ratios for Adacel divided by historical controls of > 0.66) for all 4 pertussis antigens with GMCs of 1.04 (95%CI 0.92, 1.18) for PT, 4.51 (95%CI 4.51, 6.05) for FHA, 2.94 (95%CI 2.46, 3.51) for PRN, and 2.18 (95%CI 1.84, 2.60) for FIM. The pertussis booster response rates (as defined above in the discussion of immunogenicity success criteria) met non-inferiority success criteria (LL of the 95% CI for Adacel minus historical controls of < -10%) for PT (16.12 [95%CI 13.27, 18.73]) and FHA (-4.21 [95%CI -7.23, -1.34]) but did not meet the criteria for PRN (-18.61 [95%CI -21.7, -15.6]) and FIM (-19.07 [95%CI -22.3, -16.0]). This result may have been due in part to the higher pre-vaccination GMCs for PRN (49.4 [95%CI 45.5, 53.8]) and FIM (143 [95%CI 134, 152]) versus PT (12.6 [95%CI 11.6, 13.6]) and FHA (35.4 [95%CI 33.4, 37.5]). However, the totality of immunogenicity results were deemed acceptable to support approval of this supplement, because the point estimates for GMCs for PRN and FIM were non-inferior to GMCs observed in the Sweden I study, for which clinical efficacy was demonstrated.

Safety was an observational endpoint for the study. Solicited local and systemic adverse events (AEs) were collected for 7 days following vaccination. Unsolicited adverse events were collected for 28 days following the second dose of Adacel. Serious adverse events (SAEs) were collected for 6 months following vaccination. The Safety Analysis Set included 999 subjects from the Adacel vaccine group and 328 subjects from Td Adsorbed group. Safety results are summarized in Section 7.

#### Bioresearch Monitoring

The CBER Bioresearch Monitoring (BIMO) Branch issued an inspection assignment for one foreign clinical study site that participated in the conduct of study Td537. The BIMO inspection did not reveal any issues that would impact the data submitted in this application.

### **Supportive Study Td518**

Study Td518 was a Phase IV, observational, single-arm, open-label, multicenter, study submitted to provide safety and immunogenicity to support re-administration of Adacel for management of tetanus-prone wounds. The study evaluated the safety and immunogenicity of a second dose of Adacel when administered 4 to 5 years after the first dose of Adacel. Male and female subjects 15-69 years of age were enrolled from three previous US and Canada studies; Td501, Td502 or Td505. In Td518, 545 subjects (276 subjects of age 15-22 years, 38 subjects of age 23-33 years, 163 subjects of age 34-53 years, and 68 subjects of age 54-69 years) received second dose of Adacel. Descriptive immunogenicity data for tetanus, diphtheria and pertussis were collected pre-vaccination and at 28-days post-vaccination. Safety data were collected for up to 6 months following vaccination, the results of which are presented in section 7.

For tetanus, pre-vaccination seroprotection rates (defined as  $>0.1$  IU/mL), collected at 4 to 5 years after receipt of Adacel were 96.0 (95%CI 93.7, 97.6) and highlight that some individuals sustaining a tetanus prone-wound might not be seroprotected at 5 years after receipt of a tetanus-containing vaccine. Post-vaccination seroprotection rates for tetanus were 100% (95%CI 99.2, 100).

### **Supportive Study Td506LT**

Study Td506LT, an extension of the original licensure study Td506, was designed to follow long-term antibody persistence in healthy subjects 11 through 64 years of age. It was submitted with the intent of providing evidence to support the benefit of a second booster vaccination with Adacel at 10 years. No additional vaccines were administered, no safety evaluations were conducted, and no adverse events were collected. The observational objectives were to describe the immune responses to tetanus, diphtheria, and pertussis (PT, FHA, PRN, and FIM) vaccine antigens after 1-, 3-, 5- and 10- years post vaccination with Adacel or Td Adsorbed vaccine and to compare seroprotection rates (defined as  $\geq 0.1$  IU/mL) for diphtheria and tetanus between Adacel or Td Adsorbed vaccine recipients. Out of 4450 subjects 11 through 64 years of age from the original study, Td506, 1327 subjects provided blood at the 1 year follow up visit, 1175 subjects provided blood at the 3 years follow up visit, and 917 subjects provided blood at the 5 years follow up visit. At the 10-year follow-up visit 189 Adacel recipients provided blood for immunogenicity.

At the ten-year time point, 100% of adolescents and adults were seroprotected against tetanus (95%CI 94.2, 100 and 80.5, 100, respectively). For diphtheria, 94.1% (95%CI 71.3, 99.9) of adolescents and 85.5% (95%CI 74.2, 93.1) of adults were seroprotected. Although tetanus and diphtheria GMCs decreased over time, they remained above pre-vaccination levels; pre-vaccination levels were 1.19 IU/mL (95%CI 0.71, 2.01) for tetanus and 0.17 IU/mL (95%CI 0.09, 0.32) for diphtheria in adolescents, and 1.68 IU/mL [95%CI 1.32, 2.15] for tetanus and 0.18 [95%CI 0.11, 0.29] for diphtheria in adults. For pertussis antigens FHA, PRN, and FIM, but not for PT, the GMC levels remained above the pre-vaccination levels. The ELISA assay used to measure PT antibodies at 5- and 10- years post-vaccination differed from the ELISA assay used during the original study and the earlier follow ups, thus limiting the longitudinal evaluation of these GMC results.

## **b) Pediatrics**

Evaluation of Adacel for pediatric use was not required because the applicant proposes a change in the usage of Adacel, but no change in active ingredients, indication, dosage form, dosing regimen, or route of administration. Therefore, this product remains appropriately labeled for use in all relevant pediatric populations, and PREA was not triggered for this submission.

**c) Other Special Populations**

Adacel is not approved for use in individuals 65 years of age and older.

**7. SAFETY**

**Primary Study Td537**

The subjects who received a second vaccination of Adacel were evaluated for safety outcomes in study Td537. The rates of solicited AEs monitored for 7 days post-vaccination using a diary card were comparable across the Adacel and Td Adsorbed groups. The majority of solicited injection site and systemic adverse reactions were of Grade 1 or 2 intensity. Grade 3 adverse reactions, solicited and unsolicited, were reported by less than 8% of subjects and were similar between the vaccine groups.

Injection site pain (Adacel: 87.1%; Td Adsorbed: 87.4%), myalgia (Adacel: 58.1%; Td Adsorbed: 58.2%), headache (Adacel: 41.4%; Td Adsorbed: 39.1%), and malaise (Adacel: 33.3%; Td Adsorbed: 30.8%) were the most common solicited systemic AEs. A total of 262 (26.2%) subjects in the Adacel group and 85 (25.9%) subjects in the Td Adsorbed group experienced at least one unsolicited AE. Nasopharyngitis (3.7% in Adacel and 4.6% in Td Adsorbed) and headache (3.0% in Adacel and 2.7% in Td Adsorbed) were the most common unsolicited AEs. In study Td537 total of 8 (0.8%) subjects in the Adacel group and 1 (0.3%) subject in the Td Adsorbed group reported SAEs from visit 1 to 6 months post-vaccination. Based on review of the nature and timing relative to vaccination of SAEs reported by the applicant, none were assessed as related to the study vaccine.

There were no deaths reported in study Td537. No subjects discontinued due to an SAE or other solicited or unsolicited AE. There were two pregnancies during the study, one with miscarriage (spontaneous abortion) and one live birth. The newborn had no congenital abnormalities.

**Supportive Study Td518**

Subjects who received a second dose of Adacel when administered 4 to 5 years after the first dose of Adacel were monitored for injection site and solicited systemic reactions for 14 days post-vaccination, unsolicited AEs for 28-days post-vaccination, and SAEs and new onset medically attended adverse events through 6 months post-vaccination.

The most common solicited injection site reactions were pain (87.6%), followed by erythema/redness (28.6%) and swelling (25.6%). The rates of injection site reactions were higher after second vaccination than that observed after first vaccination (76.8% for pain, 19.2% for erythema/redness, and 16.2% for swelling). The most frequently reported solicited systemic adverse reactions were myalgia (61.0%) followed by headache (53.2%), again occurring at higher rates after second vaccination compared with those observed after first vaccination (27.7% for headache and 39.7% for myalgia). Though the reactogenicity was increased following the second dose, most reactions

were mild to moderate and important differences were not observed in rates of severe injection-site or systemic solicited adverse reactions.

## **8. ADVISORY COMMITTEE MEETING**

No issues were identified during the review of the supplement that required presentation before the Vaccines and Related Biological Products Advisory Committee.

## **9. OTHER RELEVANT REGULATORY ISSUES**

No other relevant regulatory issues were identified during the review of this supplement.

## **10. LABELING**

The Adacel package insert was revised to use active voice and to avoid overuse of bullets and bolded sub-headings. The highlights were made consistent with Full Prescribing Information. The package insert was revised to include the occurrence of Arthus reactions as an adverse reaction observed in post-marketing experience (Section 6.2). The applicant was required to revise Section 8, Use in Specific Populations, to comply with the Pregnancy and Lactation Labeling Rule (PLLR). Additional revisions were made to Section 2; Dosage and Administration, Section 6; Adverse Reactions, Section 8; Use in Specific Populations, and Section 14; Clinical Studies. All labeling issues were resolved after exchange of information and discussion with the applicant.

The Advertising and Promotional Labeling Branch (APLB) found the prescribing information and carton/container labels for Adacel to be acceptable from a promotional and comprehension perspective.

## **11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT**

### **a) Recommended Regulatory Action**

Based on the reviewed safety and immunogenicity data, the review committee recommends approval of the supplement submitted by Sanofi Pasteur under BLA 125111/679. The prescribing information for Adacel can be revised to administer a second booster dose of Adacel to adults at least eight years after the first vaccination with a Tdap vaccine. For management of a tetanus prone wound, the data support administration of a booster dose of Adacel if at least 5 years have elapsed since previous receipt of a tetanus toxoid containing vaccine.

### **b) Risk/ Benefit Assessment**

With regard to risk, the submitted data did not identify important safety concerns in subjects 18 years to 64 years of age who received a second vaccination of Adacel at an interval of 8-12 years after the first vaccination with Adacel. With regard to benefit, the pertussis immune responses after the second vaccination with Adacel were non-inferior to those observed post-vaccination in DAPTACEL historical studies, and seroprotection rates for diphtheria increased from approximately 80% to greater than 99% after vaccination, providing increased protection against diphtheria disease (seroprotection rates for tetanus were 100% both pre and post-vaccination). Therefore, the risk benefit profile for a second vaccination of Adacel is found to be favorable. Regarding proposed use for wound management, although rates of local and systemic reactogenicity were higher after the second dose compared to rates observed after the first booster dose, these events were mild to moderate without clinically important imbalances in severe reactogenicity. Given the lethality of tetanus disease, and the observation that some individuals are below the threshold for protection at 5 years post-vaccination (based on 95% CIs

for pre-vaccination seroprotection rates described in study Td518), the benefits of administering a booster dose of Adacel for management of a tetanus-prone wound outweigh the risks.

**c) Recommendation for Post Marketing Activities**

Based on review of the submitted data, including absence of new or unexpected safety findings after the second vaccination of Adacel, the review committee recommended no changes to the existing routine pharmacovigilance plan for Adacel.