Summary Basis for Regulatory Action

Date: March 24, 2014

From: Christina Houck, Review Committee Chair

Through: Paul G. Richman, Ph.D., Chief, CMC Branch 1

BLA/ STN#: 125111-509

Applicant Name: Sanofi Pasteur Ltd.

Date of Submission: May 31, 2013

PDUFA Goal Date: March 31, 2014

Proprietary Name/ Established Name: Adacel®, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed

Reason for the Submission:

To lower the age indication for Adacel administration from 11 to 10 years of age.

Recommended Action: Approval

Signatory Authorities Action: Approval

Office Signatory Authority: Wellington Sun, M.D., Director, 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.**

Material Reviewed/ Consulted Reviewer Name – Document(s) Date	**Specific documentation used in developing the SBRA**	
Clinical Review	Ann T. Schwartz, M.D.	3/13/14
Statistical Review	Martha Lee, Ph.D.	1/17/2014
Serological Immune Response Assay Review Serological Immune Response Assay Review	Freyja Lynn Leslie Wagner	1/30/2014 2/16/2014

Prescribing Information	Ann T. Schwartz Maryann Gallagher	3/13/14 10/16/13
Chair/Regulatory Project Manager	Christina Houck	

1. Introduction and Background

Adacel (Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine Adsorbed) is currently indicated for active booster immunization for the prevention of tetanus, diphtheria, and pertussis infections. In 2005 Adacel was approved in the US for use in persons 11 through 64 years of age. Approval was based upon the demonstration of non-inferiority to a US-licensed tetanus and reduced diphtheria vaccine (Td-Decavac) and a bridging study showing non-inferiority of the antibody responses to pertussis antigens when compared to the antibody responses associated with protection from pertussis in the infant efficacy study. The infants studied in this comparison group had formed the cohort for the Sweden I trial in which the efficacy following three doses of Daptacel (DTaP) against World Health Organization-defined typical pertussis was demonstrated to be 85% [two-sided 95% confidence interval(CI): 81%, 89%].

The Advisory Committee on Immunization Practices recommends that all adolescents 11 through 18 years of age receive a single dose of Tdap vaccine, and states that the preferred age for Tdap vaccination is at 11 through 12 years of age. Due to the current epidemiology of pertussis, several US States have instituted a requirement that children receive Tdap vaccine before entering 6th grade or middle school. As some students are 10 years of age at school entry when Tdap vaccine is required for school enrollment, the applicant conducted a safety and immunogenicity study of Adacel vaccine in support of an extension of the licensed age indication to include children 10 years of age.

In this submission, the Applicant proposes to demonstrate the safety and immunogenicity of a single dose of Adacel vaccine in subjects 10 to < 11 years of age compared with subjects 11 to < 12 years of age to support an extension of the age indication to 10 years of age.

2. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The product formulation used in the study of Adacel in individuals 11 years through 64 years of age is identical to the formulation described in and approved with the original Adacel Biologics License Application (BLA). Therefore, no new data regarding product quality, facilities inspection or environmental assessment were provided by the applicant or reviewed in support of this supplement.

b) CBER Lot Release

There are no pending lots or issues that would preclude approval of this supplement.

c) Facilities Review/Inspection

There are no ongoing or impending investigations or compliance actions with respect to Sanofi's facilities or products. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management did not object to approval of this supplement.

3. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted as part of this supplement.

4. Clinical Pharmacology

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

5. Clinical/ Statistical

a) Clinical Program

The safety and immunogenicity of Adacel was evaluated in 1221 subjects (613 subjects, 10 to < 11 years of age and 608 subjects, 11 to < 12 years of age) in clinical study Td 519, an open-label, two arm multi-center study to support the an extension of the age indication from 11 years to 10 years of age. The primary endpoints were the evaluation of the pertussis immune responses measured as Geometric Mean Titers (GMTs) and as booster responses one month following vaccination. The third co-primary endpoint evaluated the booster response rates for diphtheria and tetanus based upon the antibody titer rise between pre- and post-vaccination samples. The assessment of seroresponse (post-vaccination titers ≥ 0.1 IU/mL) for both diphtheria and tetanus antigens were evaluated as a secondary endpoint. Safety was assessed as an observational endpoint and included the rates of immediate reactions (within 20 minutes of vaccination), solicited reactions (within 7 days post-vaccination), unsolicited AEs (within 28 days post-vaccination), and SAEs within 28 days following receipt of Adacel vaccine. CBER concurred with the clinical trial design and endpoints.
The per-protocol (PP) Analysis Set included a total of 1221 subjects (613 subjects, 10 to < 11 years of age and 608 subjects, 11 to < 12 years of age). The results of the co-primary endpoints are described below:

- The post-vaccination anti-pertussis GMTs of subjects 10 to < 11 years of age were non-inferior to the GMTs of subjects 11 to < 12 years of age, respectively, for antibodies to PT, FHA, PRN, and FIM.
- The post-vaccination anti-pertussis booster response rates for the 10 to < 11 years age group were non-inferior to the booster response rates in the 11 to < 12 years age group, respectively, for each pertussis antigen except FIM. Non-inferiority was to be supported by the data if the lower bound of the two-sided 95% CI was greater than -5% if the response rate for group 11 to < 12 years is > 95%. For anti-FIM booster responses the lower bound was -5.96, thus non-inferiority was not met.

- The post-vaccination anti-tetanus and anti-diphtheria booster response rates for the 10 to < 11 years age group were non-inferior to the booster response rates in the 11 to < 12 years age group, respectively, for both antigens.

The safety and immunogenicity data from study Td519 in 10 to <11 year olds support an update to the Adacel package insert.

Clinical Serology Assays

The following serological assays, performed by Sanofi Pastuer's Global Clinical Immunology laboratory, were used to measure immune response in subjects in Study Td519 to support this efficacy supplement:

- Response to the diphtheria vaccine antigen: Toxin ----(b)(4)------ test
- Response to the tetanus vaccine antigen: Tetanus (b)(4)
- Response to the acellular pertussis vaccine antigens:
    - Pertussis Toxin (PT) ELISA
    - Filamentous Hemagglutinin (FHA) ELISA
    - Fimbriae Types 2 and 3 (FIM) ELISA
    - Pertactin (PRN) ELISA

The methodology and validation for the ELISAs to quantitate antibodies to the pertussis antigens were previously reviewed under IND 14668. The clinical data and ELISA assay data, in support of the reported responses to the pertussis components of the vaccine, have been reviewed and the assays deemed adequate for their intended use in this supplement.

The methodology and validation of the ----------(b)(4)---------- and the ----------(b)(4)------ to quantitate the amount of ----------(b)(4)---------- were reviewed and the assays deemed adequate for the intended use in this supplement.

6. Safety

Safety was assessed following a single dose of Adacel vaccine as immediate reactions (within 20 minutes of vaccination), solicited local and systemic adverse events (days 0-7) and unsolicited adverse events from Visit 1 to Visit 2 (approximately 30 days). The majority of solicited adverse events were Grade 1 or 2 within both groups. The occurrence of Grade 3 events was similar between the two groups. The majority of unsolicited non-serious AEs were Grade 1 or 2 in intensity. Grade 3 unsolicited non-serious AEs were reported by 25 (3.8%) subjects 10 to < 11 years of age and 26 (4.0%) subjects 11 to < 12 years of age. There was one non-fatal Serious Adverse event in the 11 to < 12 year old age group that led to the subject's

discontinuation from the study. The subject experienced a right parietal occipital cerebrovascular accident on the same day as the vaccination. SAE reports indicate that the event was due to a previously unknown venous malformation. The event was not attributed to vaccination with the study product.

7. Advisory Committee Meeting

There were no issues pertaining to this supplement that required input from the Vaccines and Related Biological Products Advisory Committee.

8. Other Relevant Regulatory Issues

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

9. Labeling

The package insert (PI) was reviewed by the review committee, including the reviewer from the Advertising and Promotional Labeling Branch. All issues were acceptably resolved after exchange of information and discussions with the Applicant.

10. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

The Committee recommends approval of the Applicant's BLA supplement, which contains data supporting a labeling change to lower the age indication for Adacel administration from 11 to 10 years of age.

b) Risk/Benefit Assessment

Data submitted did not indicate that there is an increased safety risk to subjects 10 years to < 11 years receiving a single dose of Adacel vaccine when compared to children 11 to < 12 years of age. Seroprotection rates and booster response rates for diphtheria and tetanus were shown to be similar between the two age groups. There are no correlates of protection established for pertussis antibody responses. However, since immune responses in the two age groups were similar (except for the booster response to FIM in the younger age group) this supports the premise that the vaccine would be similarly effective in children 10 to < 11 years as it is in children 11 to < 12 years of age.

c) Recommendation for Postmarketing Risk Management Activities

No Postmarketing Risk Management Activities are recommended.

d) Recommendation for Postmarketing Activities

No safety signals have been identified to date that would justify a post-marketing requirement.