Summary Basis for Regulatory Action (SBRA)

Date: July 12, 2011

From: Rana Chattopadhyay, Chair of the Review Committee

BLA/ STN#: 125145/150

Applicant Name: Sanofi Pasteur Limited

Date of Submission: September 29, 2010

PDUFA Goal Date: July 30, 2011

Proprietary Name/ Established Name: Pentacel® / Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine,

Reason for the submission: To include changes to the 'Dosage and Administration' section of the package insert.

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Wellington Sun, M.D., Director Division of Vaccines and Related Products Applications, Office of Vaccine Research and Review
X 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.

Table 1: Review documents used in compiling this SBRA:

Review Category	Reviewer
Clinical/Labeling Review	Karen Farizo, M.D.
Labeling Review	Maryann Gallagher, CSO

Background
On May 14, 2002, DAPTACEL [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP)] initially was approved in the US for use as a four-dose series in children 6 weeks through 6 years of age. Subsequently, on March 12, 2008, CBER approved use of DAPTACEL as a fifth consecutive dose of DTaP in children 4 through 6 years of age who previously received four doses of DAPTACEL.

On June 20, 2008, Pentacel [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid

Conjugate) Vaccine] was approved for use as a four-dose series in children 6 weeks through 4 years of age. Pentacel and DAPTACEL contain the same pertussis antigens, manufactured by Sanofi Pasteur according to the same process, although Pentacel contains twice the amount of detoxified pertussis toxin and four times the amount of filamentous hemagglutinin as DAPTACEL. When Pentacel initially was approved, the Dosage and Administration section of the package insert stated that children who have completed a four-dose series with Pentacel should receive a fifth dose of DTaP using DAPTACEL at 4-6 years of age, although data were not available on this mixed sequence of Pentacel and DAPTACEL. The June 2008 approval letter for Pentacel included acknowledgement of a post-marketing commitment from Sanofi Pasteur to submit clinical data to support use of DAPTACEL to complete the DTaP series following four previous doses of Pentacel.

To fulfill the post-marketing commitment, on July 31, 2008, Sanofi Pasteur submitted the Integrated Clinical and Statistical Report for Study P3T10 in Pentacel Supplement STN 125145/32. In Study P3T10, the safety of DAPTACEL was evaluated in 989 children 4 through 6 years of age who had previously received four doses of Pentacel. On July 24, 2009, CBER determined that this Supplement fulfilled the post-marketing commitment from the initial approval of Pentacel. At that time, CBER requested that Sanofi Pasteur submit a Pentacel Supplement to update the Dosage and Administration section of the package insert by removing the statement that data are not available on use of DAPTACEL following a four dose series with Pentacel. CBER also requested that Sanofi Pasteur submit a DAPTACEL Supplement to revise the DAPTACEL package insert to include safety data from Study P3T10 on use of DAPTACEL following a four dose series with Pentacel.

In the evaluation of booster immunization with a DTaP vaccine, for which clinical efficacy against pertussis has been demonstrated following primary immunization of infants, CBER has required clinical safety data, but has not required clinical data on the immune responses to a booster dose following priming with the same vaccine. For diphtheria and tetanus, it is expected that most children have protective levels of antibody prior to booster immunization. With regard to pertussis, for which a serological correlate of protection has not been identified, it is assumed that children previously primed with a vaccine shown to confer protection in a clinical endpoint efficacy trial, will have a robust immune response to a booster dose of the same vaccine. In view of the relatedness of DAPTACEL and Pentacel with regard to the DTaP component, CBER also agreed to this approach in the clinical evaluation of use of DAPTACEL as a booster dose following a four-dose series with Pentacel, and required only clinical safety data.

Clinical Review of Study P3T10
Clinical review of Study P3T10 was completed under Pentacel Supplement 125145/32 (July 16, 2009 clinical review memo).

Review of Revised Pentacel Labeling
As requested by CBER, with the current Pentacel Supplement, Sanofi Pasteur has submitted a revised Pentacel package insert to remove the statement in Dosage and

Administration that data are not available on the use of DAPTACEL following a four-dose series with Pentacel, and to reference the DAPTACEL package insert regarding this dosing regimen. A revised DAPTACEL package insert to include safety data from Study P3T10 on use of DAPTACEL following a four-dose series with Pentacel is concurrently reviewed under DAPTACEL Supplement STN 103666/5254. In view of the clinical safety data from Study P3T10, Sanofi Pasteur's proposed revision to the Pentacel package insert is appropriate. The sponsor has satisfactorily addressed few minor additional CBER comments on the revised Pentacel package insert, which is acceptable for approval.

Recommendation
The committee recommends the approval of this Supplement.