July 2, 2018

Aaron Siri
Siri & Glimstad LLP
200 Park Avenue, 17th Floor
New York, NY 100166

In reply refer to file: F18-3993

Dear Mr. Siri,

This is in reply to your Freedom of Information Act (FOIA) request dated May 9, 2018, in which you requested in regards to DAPTACEL Supplement STN# 103666/5158 “a copy of the text redacted in Section 6.6.2” and “documentation providing basis for redacting Section 6.6.2.” Your request was received in the Center for Biologics Evaluation and Research on May 14, 2018.

Enclosed please find Section 6.6.2 of the DAPTACEL BLA Supplement 103666/5158 Clinical Review.

In regards to your request for “the basis for redacting Section 6.6.2,” the FOIA exemption code was not included at the time the document was posted to the FDA website, but the withheld portions of the page were redacted under Exemption (b)(4), 5 U.S.C. § 522(b)(4). That exemption permits the withholding of trade secrets and commercial or financial information that was obtained from a person outside the government and that is privileged or confidential. The withholding of such information is permitted if disclosure is likely to cause substantial competitive harm to the person who submitted the information.

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If you have any questions or if I can be of further assistance, please let me know by referencing the above file number. I can be reached by phone at 240-402-8008 or by e-mail at Ricci.Ward@fda.hhs.gov.

Sincerely,

Ricci Ward
Consumer Safety Officer
Access Litigation and Freedom of Information Branch
Center for Biologics Evaluation and Research
Food and Drug Administration

Parents/guardians were instructed to contact the study site if the DAPTACEL-injected arm appeared larger than the opposite arm. Requests to return to the clinic for evaluation were made at the discretion of the Investigator. During follow-up phone calls conducted on Days 3 and 8 post-vaccination, study personnel asked the parent/guardian to bring the child in for evaluation if the DAPTACEL-injected arm circumference had increased >20 mm over baseline.

Solicited systemic adverse events included fever (oral temperature), irritability, crying, lethargy, decreased appetite, vomiting, diarrhea, and rash. Parents/guardians were asked to call the study site for temperatures >39.5°C.

For adverse events present on Day 7, parents were instructed to record the stop date. For subjects with fever on Day 7, temperature was to be measured daily until <38.0°C.

Telephone calls were conducted on Days 3 and 8 post-vaccination to collect information on solicited adverse events from the memory aids and to inquire about unsolicited adverse events and concomitant medications.

Serious adverse events were monitored through Day 180 post-vaccination, with follow-up phone calls conducted on Days 60 and 180.

6.6.2 Immunogenicity Monitoring

Pre- and post-vaccination blood samples (approximately 5 ml each) were to be collected from a subset of at least 200 DAPTACEL-primed subjects and 75 Pentacel-primed subjects. Pre-vaccination blood samples were collected just prior to vaccination. Post-vaccination blood samples were collected 28-48 days following vaccination (Visit 2). Prior to version 5 of the protocol (dated October 18, 2005), pre- and post-vaccination serum samples were required of all subjects. With implementation of version 5 of the protocol, to enhance enrollment, serum samples were no longer collected.

If the volume of serum obtained from a subject was insufficient to perform all assays, the assays were prioritized in the following order: antibodies to pertussis antigens, diphtheria, tetanus, and polioviruses.

Micrometabolic inhibition tests (MIT) were used to measure the level of toxin-specific neutralizing antibodies to Diphtheria Toxin and the level of virus neutralizing antibodies to Poliovirus Types 1, 2, and 3. Enzyme-linked immunosorbent assays (ELISAs) were used to quantitate levels of antibody to tetanus toxoid, and to the pertussis antigens (PT, FHA, FIM and PRN).

The Tetanus IgG ELISA and the Diphtheria and Poliovirus MITs were performed by Global Clinical Immunology (GCI) at Sanofi Pasteur Inc. in Swiftwater, Pennsylvania. The pertussis IgG ELISAs were performed by the Clinical Immunology Platform (CIP) at Sanofi Pasteur Ltd. in Toronto, Ontario.

Validation of the Diphtheria, Tetanus, FHA, FIM and PRN assays used in Study P3T11 is currently considered adequate by CBER based on review under the Pentacel IND (#8502) and BLA (STN# 125145/0). Based on review under the Pentacel BLA, the anti-PT assay used in Study P3T11 is not considered acceptable by CBER because of non-specificity due to contamination of the coating antigen with fimbriae. In 2006, information on re-validation of the poliovirus assays used in Study P3T11 was submitted to Sanofi Pasteur Inc.'s IND for Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] (IND #7162, amendment 233). In E-mail correspondence from Dr. Ronald Lundquist (CBER, OVRR, Division of Viral Products) to Ms. Martha Monser (CBER, OVRR, Division of Vaccines and Related Product Applications) on 10/19/07, Dr. Lundquist indicated that there were "no obvious problems with the procedure used to validate the MIT test for poliovirus neutralizing antibodies".

Date: 3/6/08

From: Karen M. Farizo, M.D.
Medical Officer
Vaccine Clinical Trials Branch
Division of Vaccines and Related Product Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

Subject: Clinical Review of DAPTACEL Efficacy Supplement for a New Dosing Regimen to Include a Fifth Consecutive Dose

To: BLA STN# 103666/5158

Through: Lucia Lee, M.D., Team Leader
Vaccines Clinical Trials Branch

1 General Information

1.1 Medical Officer Review Identifiers and Dates

1.1.1 BLA Supplement #: 103666/5158

1.1.2 Related INDs and BLAs:

- DAPTACEL [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP), Sanofi Pasteur Limited] IND #----
- ADACEL [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap), Sanofi Pasteur Limited] IND #----; BLA STN# 125111 (approved as a single booster dose in persons 11 through 64 years of age).
- Pentacel [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus and *Haemophilus* b Conjugate (Tetanus Toxoid Conjugate) Vaccine, Sanofi Pasteur Limited] IND #----; BLA STN #------ (BLA for use as a four dose series in children 6 weeks through 6 years of age currently under review by CBER).

1.1.3 Reviewer Name, Division, and Mail Code

Karen Farizo, M.D.
Division of Vaccines and Related Products Applications
HFM-475

1.1.4 Submission Received by FDA: 5/17/07

1.2 Product

1.2.1 Proper Name: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

1.2.2 Tradename: DAPTACEL

1.2.3 Product Formulation (per 0.5 mL dose):

Active Ingredients:
10 µg Pertussis Toxoid (PT)
5 µg Filamentous hemagglutinin (FHA)
5 µg Fimbriae 2 & 3 (FIM)
3 µg Pertactin (PRN)
15 LF Diphtheria toxoid
5 LF Tetanus toxoid
Adjuvant: 0.33 mg aluminum
Excipient: 0.6% 2-phenoxyethanol

1.3 Applicant: Sanofi Pasteur Limited

1.4 Pharmacologic Class: Vaccine

1.5 Proposed Indications:

DAPTACEL is currently indicated for active immunization against diphtheria, tetanus, and pertussis in infants and children 6 weeks through 6 years of age (prior to seventh birthday). The current dosing regimen for DAPTACEL is a four dose series, administered

at 2, 4, 6, and 15-20 months of age. With this Supplement, the applicant is requesting approval of a fifth consecutive dose of DAPTACEL, to be administered at 4-6 years of age.

1.6 Dosage Forms and Routes of Administration: DAPTACEL is a suspension supplied in single dose vials and administered intramuscularly. There are no new proposed dosage forms or routes of administration.

1.7 Revisions to Package Insert: With this Supplement, the applicant has submitted a revised package insert in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006.

2 Table of Contents

3 Executive Summary

Background

In May 2002, DAPTACEL was approved as a four dose series for children ages 6 weeks through 6 years. Three doses of DAPTACEL constitute a primary immunization series for diphtheria and tetanus. Four doses of DAPTACEL constitute a primary immunization series for pertussis. The current approved schedule for DAPTACEL is a single dose administered at 2, 4, 6, and 15-20 months of age. Approval of DAPTACEL for children through 6 years of age was intended to allow catch-up immunization for children who had delayed vaccinations for the first four doses of the DTaP series and to allow use of DAPTACEL to complete the immunization series in children who had received one or more doses of whole-cell pertussis DTP vaccine. The Advisory Committee on Immunization Practices (ACIP) recommends that infants and children routinely receive five doses of DTaP vaccine, with the fifth dose administered at 4-6 years of age. At the time of approval of DAPTACEL, data were not available to support use of a fifth consecutive dose of DAPTACEL.

The May 14, 2002 approval letter for DAPTACEL included a clinical commitment to conduct a study to assess the use of DAPTACEL as a fifth dose at 4-6 years of age following four previous doses of DAPTACEL. This Supplement contains clinical data from Study P3T11, which was conducted to fulfill this post-marketing commitment. With this Supplement, the applicant is requesting approval of a fifth dose of DAPTACEL following four previous doses of DAPTACEL.

For DTaP vaccines already approved for a primary series, CBER has based decisions regarding approval of booster doses following a primary series of the same vaccine solely on safety data. In these instances, CBER has not required evaluation of the immune response to booster doses of DTaP vaccines.

Safety

In this Supplement, safety data on administration of DAPTACEL at 4-6 years of age were provided from one study, Study P3T11. In this study, 649 subjects received a dose of DAPTACEL, including 487 subjects who previously received four doses of DAPTACEL and 162 subjects who previously received four doses of Pentacel, which is not currently licensed in the U.S. Pentacel consists of two licensed components, POLIOVAX [Inactivated Poliovirus Vaccine (IPV), Sanofi Pasteur Limited] and ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur SA] and an unlicensed DTaP component. The DTaP component of Pentacel is the same as DAPTACEL except that it contains ---------- ---------- PT and ---------- FHA. The safety data on Pentacel primed subjects from Study P3T11 are considered supportive for the evaluation of the safety of a fifth consecutive dose of DAPTACEL.

In Study P3T11, all subjects received the second dose of measles, mumps, and rubella vaccine (MMR) concomitantly with DAPTACEL. DAPTACEL primed subjects also received the fourth dose of inactivated poliovirus vaccine (IPV) concomitantly with the fifth dose of DAPTACEL.

Study P3T11 subjects were a non-random subset (approximately 40%) of subjects who received four doses of DAPTACEL or Pentacel in a previous study, Study P3T06. Study P3T11 subjects appeared to be representative of subjects who participated in the earlier four-dose study with regard to solicited local and systemic adverse events following the fourth dose of DAPTACEL or Pentacel.

Overall, approximately 70-75% of subjects in Study P3T11 reported at least one solicited local reaction within 0-3 days following DAPTACEL administered as the fifth dose of DTaP at 4-6 years of age. Among subjects who received a fifth consecutive dose of DAPTACEL, within 0-3 days post-vaccination, reported rates of injection site tenderness, redness, and swelling of any severity were approximately 62%, 36%, and 24%, respectively. In these subjects, the rates of incapacitating tenderness, redness >50 mm, and swelling >50 mm were approximately 2%, 16%, and 8%, respectively. During the period 0-3 days post-vaccination,

among DAPTACEL-primed subjects, approximately 38% and 1.5% reported an increase in the circumference of the DAPTACEL-injected arm of >5 mm and >40 mm, respectively. During this period, among DAPTACEL-primed subjects, approximately 20% reported some interference with normal activity of the injected arm, including 0.4% who reported interference that was incapacitating, resulted in inability to move the arm, or required medical care or absenteeism.

Overall in Study P3T11, rates of local reactions tended to be higher following DAPTACEL administered as the fifth dose of DTaP compared with rates observed following Doses 1-4 of DAPTACEL or Pentacel in Study P3T06. This finding is consistent with available data on other U.S. licensed DTaP vaccines for which the fifth consecutive dose has been associated with higher rates of local adverse events compared with previous doses.[1, 2] Among the 649 subjects who received DAPTACEL at 4-6 years of age in Study P3T11, there were no unsolicited reports of extensive or entire limb swelling.

In contrast to local reactions, rates of solicited systemic reactions, including fever, tended to be lower following DAPTACEL administered as the fifth dose of DTaP (in Study P3T11), relative to previous doses of either DAPTACEL or Pentacel (in Study P3T06). In Study P3T11, the most frequently reported solicited systemic adverse event within 0-3 days after receipt of DAPTACEL was irritability, reported in approximately 25-35% of subjects.

Among the 649 subjects who received DAPTACEL in Study P3T11, there were two reports of serious adverse events within 30 days following vaccination: one case of hypoxia and bronchospasm with onset of symptoms nine days post-vaccination and one case of immune thrombocytopenia in a subject with onset of bruising prior to vaccination. The nature and timing of these events did not suggest a causal relationship with vaccination. In previous clinical studies of DAPTACEL, serious adverse events were evaluated in approximately 5,000 children who received three or four consecutive doses of DAPTACEL.[3]

Immunogenicity

This Supplement contains data on the immune response to DAPTACEL administered following four previous doses of either DAPTACEL or Pentacel, and on the immune response to the fourth dose of IPV. The immunogenicity data are presented in this review, ----------
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Recommendations

The available safety data on DAPTACEL administered as the fifth dose of DTaP in subjects previously primed with either four doses of DAPTACEL or Pentacel, combined with previous clinical experience in subjects who received three or four consecutive doses of DAPTACEL, support a recommendation for approval of a fifth consecutive dose of DAPTACEL.

4 Clinical and Regulatory Background

4.1 Diseases to be Prevented and Available Interventions

With this Supplement, the applicant is seeking approval of DAPTACEL as a fifth consecutive (booster) dose in children who previously received four doses of DAPTACEL. DAPTACEL is currently approved as a four dose series for active immunization against diphtheria, tetanus, and pertussis in infants and children 6 weeks through 6 years of age. The current approved schedule for DAPTACEL is a single dose at ages 2, 4, 6, and 15-20 months. When DAPTACEL was initially approved, the indication through 6 years of age was intended to allow catch-up immunization for children who had delayed vaccinations for the first four doses of the DTaP series and to allow use of DAPTACEL to complete the immunization series in children who had received one or more doses of whole-cell pertussis DTP vaccine. At that time, data were not available to support approval of a fifth consecutive dose of DAPTACEL. The ACIP currently recommends that infants and children routinely receive five doses of DTaP vaccine, with the fifth dose administered at age 4-6 years.

Currently, in the U.S., two DTaP vaccines (Tripedia, Sanofi Pasteur Inc. and INFANRIX, GlaxoSmithKline) are approved for a fifth consecutive dose following four previous doses of the same vaccine. INFANRIX is also approved to complete the five dose DTaP series in children who have received three doses of Pediarix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined (GlaxoSmithKline)].

In the U.S., none of the licensed DTaP vaccines or DTaP-containing combination vaccines is approved for use following one or more doses of another manufacturer's DTaP vaccine because of insufficient data to support the safety and efficacy of such regimens.

4.2 Regulatory Background Information

The May 14, 2002 approval letter for DAPTACEL included a commitment to conduct a study to assess the use of DAPTACEL as a fifth dose at 4-6 years of age following four previous doses of DAPTACEL. This Supplement contains clinical data from Study P3T11, which was conducted to fulfill this post-marketing commitment. With this Supplement, the applicant is requesting approval of a fifth dose of DAPTACEL following four previous doses of DAPTACEL. The Supplement was received by CBER on 5/17/07.

For DTaP vaccines already approved for a primary series, CBER has based decisions regarding approval of booster doses following a primary series of the same vaccine on safety data. In these instances, CBER has not required evaluation of the immune response to booster doses of DTaP vaccines.

Some of the subjects enrolled in Study P3T11 previously received four doses of Pentacel (not licensed in the U.S.). Pentacel consists of two licensed components, POLIOVAX and ActHIB, and an unlicensed DTaP component. The DTaP component of Pentacel is the same as DAPTACEL except that it contains ---- ---------- PT and ---------- FHA. The safety data on Pentacel primed subjects from Study P3T11 are considered supportive for the evaluation of the safety of a fifth consecutive dose of DAPTACEL.

5 Clinical Data Sources and Review Strategy

5.1 Material Reviewed

The primary source of data for this review was the final study report for Study P3T11 (p3t11.pdf) submitted with the original Supplement. Study P3T11 was conducted under DAPTACEL IND ----. In sections of this review, some of the data from Study P3T11 are presented and discussed in the context of previous experience with DAPTACEL. Sources of data on previous clinical experience with DAPTACEL will be

noted in the review.

5.2 Review Strategy

In Study P3T11, subjects previously vaccinated with either four doses of DAPTACEL or four doses of Pentacel received a dose of DAPTACEL at 4-6 years of age and were evaluated for safety and immunogenicity. The Supplement includes safety and immunogenicity data from both arms of the study. For regulatory decisions regarding the approvability of a fifth consecutive dose of DAPTACEL, only the safety data from the DAPTACEL primed subjects are considered essential. The safety data from the Pentacel primed subjects provide additional supportive data for evaluation of the safety of a fifth consecutive dose of DAPTACEL. As mentioned previously in Section 4.2, CBER has not required immunogenicity data to support approval of booster doses of DTaP vaccines following an already approved primary series with the same vaccine. ----------

6. Clinical Study Protocol Number and Title

Study P3T11: Safety and Immunogenicity of DAPTACEL Administered as a 5th Dose in 4- to 6-Year-Old Children Previously Immunized with DAPTACEL or Pentacel.

6.1 Rationale/Objectives

Study P3T11 was conducted to evaluate the safety and immunogenicity of a fifth dose of DAPTACEL administered following four previous doses of either DAPTACEL or Pentacel.

6.2 Design Overview

Study P3T11 was an open-label, two-arm, descriptive, multi-center study conducted in the U.S.

6.3 Population

6.3.1 Study Period

The study period was March 30, 2005 through September 22, 2006.

6.3.2 Study Sites and Recruitment

Study P3T11 was conducted at 22 of the 31 study centers that previously participated in Study P3T06. In Study P3T06, subjects received either DAPTACEL + ActHIB + IPOL (U.S. licensed IPV manufactured by Sanofi Pasteur) or Pentacel, administered at 2, 4, 6 and 15-17 months of age. In Study P3T06, U.S. licensed Prevnar [Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)], RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant)], M-M-R_{II} (Measles, Mumps, and Rubella Virus Vaccine Live), and VARIVAX [Varicella Virus Vaccine Live (Oka/Merck)] were administered according to approved schedules.

In Study P3T06, subjects were enrolled as infants to receive four consecutive doses of either DAPTACEL or Pentacel. When subjects who previously received four doses of DAPTACEL or Pentacel in Study P3T06 (approximately 1,200 and 400, respectively) were 4 to 6 years of age, parents or guardians were asked to enroll their child in Study P3T11. It was expected that approximately 50% of subjects (i.e., 600 subjects who previously received four doses of DAPTACEL and 200 subjects who previously received four doses of Pentacel) would be available and eligible for Study P3T11. Enrollment was to continue until at least 600 DAPTACEL-primed subjects and 200 Pentacel-primed subjects agreed to participate. If these enrollment numbers were not reached, enrollment was to continue until all eligible subjects were offered the opportunity to participate.

6.3.3 Inclusion Criteria

- Aged $\geq$4 years and <7 years.

- Signed and dated IRB-approved informed consent from a parent or legally authorized representative
- Judged to be in good health on the basis of reported medical history and physical exam
- Able and willing to attend the scheduled visits and to comply with study procedures
- Four previous doses of DAPTACEL or Pentacel administered in Study P3T06

6.3.4 Exclusion Criteria

- Received a 5th dose of DTaP-containing vaccine
- For subjects in the DAPTACEL arm: received a 4th dose of IPV and/or a 2nd dose of MMR
- For subjects in the Pentacel arm: received a 2nd dose of MMR
- History of severe hypersensitivity to any component of the vaccine
- Serious underlying chronic disease, including, but not limited to, diabetes mellitus; malignancy; cardiopulmonary disease; renal, endocrinologic, or hepatic dysfunction; or hematologic disorder; or unstable or evolving neurologic disorders that may predispose to seizures or neurologic deterioration
- Known or suspected primary or acquired disease of the immune system
- Receipt of blood or blood products or immunoglobulin within the past 3 months
- Injected or oral corticosteroids or other immunomodulatory therapy within 6 weeks of the study vaccine. Individuals on a tapering dose of oral steroids lasting <7 days could be included in the study as long as they had not received more than one course within the last two weeks prior to enrollment.
- Had allergy shots started or had changes in regimen or dosing of allergy shots within the last 4 weeks
- Any condition, which in the opinion of the investigator, would interfere with evaluation of the vaccine or pose a health risk to the subject
- Receipt of any other vaccine within past 30 days, or planned receipt of another vaccine within 30 days before the Visit 2 blood draw
- Enrolled in another vaccine trial
- Personal history of physician-diagnosed or laboratory-confirmed pertussis within past 30 months
- Known or suspected allergy to any vaccine or vaccine components intended for use in this study

6.3.5 Contraindications

Oral temperature $\geq$38°C ($\geq$100.4°F) and any moderate or severe acute illness with or without fever were considered temporary contraindications to vaccination. Subjects with these conditions could be subsequently re-scheduled for vaccination.

Definite contraindications to vaccination included encephalopathy within 7 days following vaccination; severe hypersensitivity to any study vaccine component; known or suspected impairment of the immune system; and progressive neurological disorder.

6.3.6 Concomitant Vaccines and Medications

Other than study vaccines, no other vaccines were to be given 30 days before Visit 1 and 30 days after DAPTACEL vaccination. If other licensed vaccines were recommended (e.g., influenza), preferably, they were to be given at least 30 days after Visit 1 and after the Visit 2 blood draw.

All prescription and over the counter medications administered during the first seven days post-vaccination were captured on the memory aid. Information was collected on use of prescription medications during the entire study period (through the 6-month safety follow-up). Antipyretics or analgesics were not given routinely pre- or post-vaccination.

6.4 Products Mandated by the Protocol

Subjects received DAPTACEL, by intramuscular injection, in the left deltoid. The fourth dose of IPOL (for DAPTACEL primed subjects only) given subcutaneously or intramuscularly and the second dose of MMR

vaccine (MMR_{II}, Merck & Co., Inc.) given subcutaneously, were administered in the right deltoid, concomitantly with DAPTACEL.

DAPTACEL lot C2207AA and IPOL lot Y0264-3 were used in Study P3T11. MMR_{II} lots were not specified.

6.5 Primary Endpoints
The safety and immunogenicity endpoints listed in Sections 6.5.1 and 6.5.2 were referred to as primary parameters measured. All primary analyses were descriptive. There were no pre-specified safety or immunogenicity hypotheses or formal hypothesis testing.

6.5.1 Safety Endpoints
- Immediate reactions
- Solicited local and systemic reactions occurring through Day 7 post-vaccination
- Unsolicited adverse events occurring through Day 7 post-vaccination
- Serious adverse events that occurred through Day 180 post-vaccination
- Adverse events that resulted in a hospital admission, life-threatening episode, medical condition that required three or more office or emergency room visits, and diagnosis of low blood count or low platelet count, swelling or redness of the joints, asthma, diabetes, or autism through Day 180 days post-vaccination

6.5.2 Immunogenicity Endpoints
Anti-pertussis (PT, FHA, FIM, and PRN) antibodies
- GMTs pre- and post-dose 5
- Percent of subjects achieving a 4-fold rise (post dose 5/pre dose 5) in antibody titers
- Geometric mean fold rise (post dose 5/pre dose 5)
- Percent of subjects achieving a booster response, defined as:
    - If pre-dose 5 antibody concentration <4X LOQ, then a 4-fold rise
    - If pre-dose 5 antibody concentration $\geq$4X LOQ, then a 2-fold rise
- Reverse cumulative distribution curves (RCDC) post-dose 5

Anti-diphtheria and anti-tetanus antibodies
- GMTs pre- and post-dose 5
- Rates of seroprotection pre-dose 5 ($\geq$0.01, $\geq$0.1, and $\geq$1.0 IU/mL) and post-dose 5 ($\geq$0.1, and $\geq$1.0 IU/mL)
- RCDC post-dose 5

6.6 Surveillance/Monitoring

6.6.1 Safety Monitoring
Study personnel observed subjects for 30 minutes post-vaccination.

Parents or guardians used a memory aid to record information on solicited local and systemic adverse events, and any adverse event that represented a change in health status, daily, on Days 0-7 post-vaccination. Solicited local adverse events at the DAPTACEL injected arm included redness, swelling, tenderness, increased arm circumference, and interference with use of the arm. Sizes of local redness, swelling and arm circumference were measured daily. Study personnel measured the circumference of the DAPTACEL-injected arm immediately prior to vaccination to obtain a baseline measurement.

Parents/guardians were instructed to contact the study site if the DAPTACEL-injected arm appeared larger than the opposite arm. Requests to return to the clinic for evaluation were made at the discretion of the Investigator. During follow-up phone calls conducted on Days 3 and 8 post-vaccination, study personnel asked the parent/guardian to bring the child in for evaluation if the DAPTACEL-injected arm circumference had increased >20 mm over baseline.

Solicited systemic adverse events included fever (oral temperature), irritability, crying, lethargy, decreased appetite, vomiting, diarrhea, and rash. Parents/guardians were asked to call the study site for temperatures >39.5^{o}C.

For adverse events present on Day 7, parents were instructed to record the stop date. For subjects with fever on Day 7, temperature was to be measured daily until <38.0^{o}C.

Telephone calls were conducted on Days 3 and 8 post-vaccination to collect information on solicited adverse events from the memory aids and to inquire about unsolicited adverse events and concomitant medications.

Serious adverse events were monitored through Day 180 post-vaccination, with follow-up phone calls conducted on Days 60 and 180.

6.6.2 ----------

[This section determined not to be releasable]

[ ]

[ ]

6.7 Statistical Considerations

The sample size of subjects who received a fifth consecutive dose of DAPTACEL in Study P3T11 depended on the number of subjects who received four doses of DAPTACEL in Study P3T06 (~1,200), who remained in the study area, and were willing to participate in Study P3T11. Prior to the study, the sponsor estimated that approximately 600 DAPTACEL primed subjects from Study P3T06 would participate in Study P3T11.

Safety and immunogenicity analyses were primarily descriptive. There was no pre-specified hypothesis testing of safety and immunogenicity outcomes.

The safety analyses were based on the Intent-to-Treat (ITT) Population for Safety, which consisted of all subjects who received DAPTACEL at Visit 1 in Study P3T11.

The primary immunogenicity analyses were based on the Per Protocol (PP) Immunogenicity Population, which consisted of subjects who satisfied the following criteria:

- Met all inclusion and exclusion criteria.
- Received the correct dose of vaccines at Visit 1.
- Had post-vaccination blood draw within 28 to 48 days after Visit 1 vaccination, with a valid serology result for at least one antigen contained in DAPTACEL.

The ITT Immunogenicity Population consisted of subjects who were vaccinated at Visit 1, who had the Visit 2 blood draw and a valid serology test result for at least one antigen contained in DAPTACEL.

6.8 Results

6.8.1 Populations Enrolled/Analyzed

A total of 1,245 subjects received 4 doses of DAPTACEL and 426 subjects received 4 doses of Pentacel in Study P3T06 and were eligible to enroll in Study P3T11. Of eligible subjects, 487 subjects (39.1%) who had received DAPTACEL in Study P3T06 and 162 subjects (38.0%) who had received Pentacel in Study P3T06, received a dose of DAPTACEL in Study P3T11. Table 1 provides a summary of subject disposition.

Table 1. Study P3T11 Summary of subject disposition

Safety Disposition	DAPTACEL Primed n (%)	Pentacel Primed n (%)
Received 4 Doses of DAPTACEL or Pentacel in Study P3T06	1245	426
Received DAPTACEL as 5th DTaP dose in Study P3T11[1]	487 (39.1)	162 (38.0)
Did not receive DAPTACEL in Study P3T11[2]	760 (61.0)	264 (62.0)
Intent-To-Treat (ITT) Safety Population[3]	487	162
Completed 180-day Safety Follow-up after Dose 5	477 (97.9)	159 (98.1)
Did not complete 180-day Safety Follow-up[4]	10 (2.1)	3 (1.9)
Did not Complete 180-day Safety Follow-up[4]	10 (100.0)	3 (100.0)
Adverse Event	0 (0.0)	0 (0.0)
Contraindication	0 (0.0)	0 (0.0)
Lost to follow-up	3 (30.0)	1 (33.3)
Non-compliance	6 (60.0)	2 (66.7)
Voluntary withdrawal	1 (10.0)	0 (0.0)
Immunology Disposition		
Received DAPTACEL as 5th DTaP Dose	487 (100.0)	162 (100.0)
Not bled post-Dose 5	224 (46.0)	79 (48.8)
Bled post-Dose 5	263 (54.0)	83 (51.2)
Received DAPTACEL as Dose 5 and Bled Post-Dose 5	263 (100.0)	83 (100.0)
ITT Immunogenicity Population[5]	262 (99.6)	83 (100.0)
Received Dose 5 and Bled Post-Dose 5 but Excluded from ITT Immunogenicity Population	1 (0.4)	0 (0.0)
Received Dose 5 and Bled Post-Dose 5 but Excluded from ITT Immunogenicity Population[6]	1 (100.0)	0 (0.0)
Invalid test result (QNS, or NS, or NR) for all antigens	1 (100.0)	0 (0.0)
ITT Immunogenicity Population[5]	262 (100.0)	83 (100.0)
Per-Protocol (PP) Immunogenicity Population[7]	255 (97.3)	81 (97.6)
Protocol violators in ITT Immunogenicity Population	7 (2.7)	2 (2.4)
Protocol Violators in ITT Immunogenicity Population[8]	7 (100.0)	2 (100.0)
Did not satisfy eligibility criteria	0 (0.0)	1 (50.0)
Visit out of time interval or age window	7 (100.0)	1 (50.0)

[1]Subjects 007-00008 and 014-00018 were not eligible for P3T11 (treatment errors in P3T06) but received DAPTACEL at Dose 5.
[2]Subject 009-00019 was enrolled in P3T11 but withdrawn prior to vaccination due to seizure post-blood draw.
[3]ITT Safety Population: Defined as subjects enrolled in the trial who received DAPTACEL at Dose 5.
[4]Subjects terminated at anytime between receipt of Dose 5 and the post-Dose 5 1 80-day safety follow-up; Only one primary reason for termination per subject is selected in the order listed.
[5]ITT Immunogenicity Population: Defined as those who had DAPTACEL as Dose 5 and a valid serology test result for at least 1 DAPTACEL antigen at post-Dose 5; As per study design, only 200 DAPTACEL-primed subjects were intended to be bled.
[6]Percentages are based on the number of subjects excluded from the ITT Immunogenicity Population. QNS=bled, but serum quantity not sufficient to perform assay; NS=bled, but serum sample not available in laboratory (broken/spilled/lost in transit); NR=bled, but test result not reportable.
[7]PP Immunogenicity Population: Defined as eligible subjects who had DAPTACEL as Dose 5, had the dose and post-Dose 5 blood drawn within windows, and had a valid serology test result for at least 1 DAPTACEL antigen at post-Dose 5.
[8]Percentages are based on the number of protocol violators in the ITT Immunogenicity Population. Only one primary reason for Protocol violation per subject is selected in the order listed.
Source: p3t11.pdf, pages 69-70

Table 2 provides a summary of subject demographics.

Table 2. Study P3T11 Summary of subject demographics, safety population

Demographic Attribute	DAPTACEL-Primed (N=487)	Pentacel-Primed (N=162)
Sex	N (%)	n (%)
Male	243 (49.9)	79 (48.8)
Female	244 (50.1)	83 (51.2)
Age (Years)		
Mean (±Standard Deviation)	4.1 (±0.14)	4.1 (±0.16)
Range	(4.0, 4.8)	(4.0, 4.7)
Race	N (%)	n (%)
Caucasian	412 (84.6)	133 (82.1)
Black	11 (2.3)	7 (4.3)
Hispanic	15 (3.1)	7 (4.3)
Asian	4 (0.8)	0 (0.0)
Other	45 (9.2)	15 (9.3)

Source: p3t11.pdf, page 71

The Supplement included analyses to evaluate whether Study P3T11 participants were representative of all eligible subjects from Study P3T06 with regard to the occurrence of solicited local and systemic adverse events post-dose 4 DAPTACEL or Pentacel in Study P3T06. Tables 3 and 4 present these analyses for DAPTACEL primed subjects from Study P3T06. Tables 5 and 6 present these analyses for Pentacel primed subjects from Study P3T06.

Table 3. Number (percentage) of subjects with solicited local reactions 0-7 days after dose 4 DAPTACEL, by participation in Study P3T11, DAPTACEL-primed subjects from Study P3T06, safety population.

Reaction/Severity	Enrolled in Study P3T11 n/N % (95% CI)	Not Enrolled in Study P3T11 n/N % (95% CI)	Total n/N % (95% CI)
Redness			
Any (>5 mm)	79/455 (17.4) (14.0, 21.2)	118/681 (17.3) (14.6, 20.4)	197/1136 (17.3) (15.2, 19.7)
Mild (>5-<25 mm)	39/455 (8.6) (6.2, 11.5)	51/681 (7.5) (5.6, 9.7)	90/1136 (7.9) (6.4, 9.6)
Moderate (25-50 mm)	28/455 (6.2) (4.1, 8.8)	44/ 681 (6.5) (4.7, 8.6)	72/1136 (6.3) (5.0, 7.9)
Severe (>50 mm)	12/455 (2.6) (1.4, 4.6)	23/ 681 (3.4) (2.2, 5.0)	35/1136 (3.1) (2.2, 4.3)
Swelling			
Any (>5 mm)	50/455 (11.0) (8.3, 14.2)	83/680 (12.2) (9.8, 14.9)	133/1135 (11.7) (9.9, 13.7)
Mild (>5-<25 mm)	31/455 (6.8) (4.7, 9.5)	48/680 (7.1) (5.3, 9.3)	79/1135 (7.0) (5.5, 8.6)
Moderate (25-50 mm)	13/455 (2.9) (1.5, 4.8)	23/680 (3.4) (2.2, 5.0)	36/1135 (3.2) (2.2, 4.4)
Severe (>50 mm)	6/455 (1.3) (0.5, 2.8)	12/680 (1.8) (0.9, 3.1)	18/1135 (1.6) (0.9, 2.5)
Tenderness*			
Any	216/456 (47.4) (42.7, 52.1)	351/684 (51.3) (47.5, 55.1)	567/1140 (49.7) (46.8, 52.7)
Mild	154/456 (33.8) (29.4, 38.3)	248/684 (36.3) (32.6, 40.0)	402/1140 (35.3) (32.5, 38.1)
Moderate	50/456 (11.0) (8.2, 14.2)	90/684 (13.2) (10.7, 15.9)	140/1140 (12.3) (10.4, 14.3)
Severe	12/456 (2.6) (1.4, 4.6)	13/684 (1.9) (1.0, 3.2)	25/1140 (2.2) (1.4, 3.2)
Change in Limb Circumference			
Any (>5 mm)	135/448 (30.1) (25.9, 34.6)	208/671 (31.0) (27.5, 34.7)	343/1119 (30.7) (28.0, 33.4)
Mild (>5-<20 mm)	106/448 (23.7) (19.8, 27.9)	155/671 (23.1) (20.0, 26.5)	261/1119 (23.3) (20.9, 25.9)
Moderate (20-40 mm)	28/448 (6.3) (4.2, 8.9)	50/671 (7.5) (5.6, 9.7)	78/1119 (7.0) (5.5, 8.6)
Severe (>40 mm)	1/448 (0.2) (0.0, 1.2)	3/671 (0.4) (0.1, 1.3)	4/1119 (0.4) (0.1, 0.9)

Each subject is counted once and classified according to the highest recorded severity score; 'n' is the number of subjects with the indicated reaction and 'N' is the number of subjects with available data from the Safety Population. Two DAPTACEL primed subjects who received Pentacel at Dose 4 and are not included.

*Mild = subject whimpers when site is touched, no crying; Moderate = subject cries when site is touched; Severe = subject cries when leg or arm is moved.
Source: p3t11.pdf, page 157; DAPTACEL package insert approved November 2006.

Table 4. Number (percentage) of subjects with solicited systemic reactions 0-7 days after dose 4 DAPTACEL, by participation in Study P3T11, DAPTACEL-primed subjects from Study P3T06, safety population.

Reaction/Severity	Enrolled in Study P3T11 n/N % (95% CI)	Not Enrolled in Study P3T11 n/N % (95% CI)	Total n/N % (95% CI)
Fever*			
>=38.0 °C	75/ 453 (16.6) (13.3, 20.3)	105/ 684 (15.4) (12.7, 18.3)	180/1137 (15.8) (13.8, 18.1)
>=38.0 °C - <=38.5 °C	43/ 453 (9.5) (7.0, 12.6)	63/ 684 (9.2) (7.2, 11.6)	106/1137 (9.3) (7.7, 11.2)
>38.5 °C - <=39.5 °C	25/ 453 (5.5) (3.6, 8.0)	30/ 684 (4.4) (3.0, 6.2)	55/1137 (4.8) (3.7, 6.3)
>39.5 °C	7/ 453 (1.5) (0.6, 3.2)	12/ 684 (1.8) (0.9, 3.0)	19/1137 (1.7) (1.0, 2.6)
Fussiness†			
Any	267/ 458 (58.3) (53.6, 62.9)	390/ 686 (56.9) (53.0, 60.6)	657/1144 (57.4) (54.5, 60.3)
Mild	159/ 458 (34.7) (30.4, 39.3)	236/ 686 (34.4) (30.8, 38.1)	395/1144 (34.5) (31.8, 37.4)
Moderate	88/ 458 (19.2) (15.7, 23.1)	117/ 686 (17.1) (14.3, 20.1)	205/1144 (17.9) (15.7, 20.3)
Severe	20/ 458 (4.4) (2.7, 6.7)	37/ 686 (5.4) (3.8, 7.4)	57/1144 (5.0) (3.8, 6.4)
Inconsolable Crying†			
Any	189/ 458 (41.3) (36.7, 45.9)	274/ 686 (39.9) (36.3, 43.7)	463/1144 (40.5) (37.6, 43.4)
Mild	133/ 458 (29.0) (24.9, 33.4)	204/ 686 (29.7) (26.3, 33.3)	337/1144 (29.5) (26.8, 32.2)
Moderate	44/ 458 (9.6) (7.1, 12.7)	59/ 686 (8.6) (6.6, 11.0)	103/1144 (9.0) (7.4, 10.8)
Severe	12/ 458 (2.6) (1.4, 4.5)	11/ 686 (1.6) (0.8, 2.9)	23/1144 (2.0) (1.3, 3.0)
Decreased Activity§			
Any	135/ 458 (29.5) (25.3, 33.9)	196/ 686 (28.6) (25.2, 32.1)	331/1144 (28.9) (26.3, 31.7)
Mild	73/ 458 (15.9) (12.7, 19.6)	121/ 686 (17.6) (14.9, 20.7)	194/1144 (17.0) (14.8, 19.3)
Moderate	53/ 458 (11.6) (8.8, 14.9)	65/ 686 (9.5) (7.4, 11.9)	118/1144 (10.3) (8.6, 12.2)
Severe	9/ 458 (2.0) (0.9, 3.7)	10/ 686 (1.5) (0.7, 2.7)	19/1144 (1.7) (1.0, 2.6)

Each subject is counted once and classified according to the highest recorded severity score; 'n' is the number of subjects with the indicated reaction and 'N' is the number of subjects with available data from the Safety Population. Two DAPTACEL primed subjects who received Pentacel at Dose 4 and are not included.
*In Study P3T06, the protocol specified that temperatures should be measured rectally. Based on all DAPTACEL subjects in Study P3T06, irrespective of participation in Study P3T11, for Dose 4, 35.7% of temperatures were measured rectally, 62.3% were measured axillary, 1.5% were measured orally, and 0.5% were measured by an unspecified route. Fever is based upon actual temperatures recorded with no adjustments to the measurements for route.
†Mild = <1hour; Moderate = 1-3 hours; Severe = >3 hours.
§Mild = Usual daily activity is not affected; Moderate = Interferes with and limits usual daily activity; Severe = Disabling, not interested in usual daily activity.
Source: p3t11.pdf, page 162; DAPTACEL package insert approved November 2006.

Table 5. Number (percentage) of subjects with solicited local reactions 0-7 days after dose 4 Pentacel, by participation in Study P3T11, Pentacel primed subjects from Study P3T06, safety population.

Reaction/Severity	Enrolled in Study P3T11 n/N % (95% CI)	Not Enrolled in Study P3T11 n/N % (95% CI)	Total
Redness			
Any (>5 mm)	24/ 149 (16.1) (10.6, 23.0)	43/ 243 (17.7) (13.1, 23.1)	67/ 392 (17.1) (13.5, 21.2)
Mild (>5-<25 mm)	11/ 149 (7.4) (3.7, 12.8)	21/ 243 (8.6) (5.4, 12.9)	32/ 392 (8.2) (5.7, 11.3)
Moderate (25-50 mm)	12/ 149 (8.1) (4.2, 13.6)	14/ 243 (5.8) (3.2, 9.5)	26/ 392 (6.6) (4.4, 9.6)
Severe (>50 mm)	1/ 149 (0.7) (0.0, 3.7)	8/ 243 (3.3) (1.4, 6.4)	9/ 392 (2.3) (1.1, 4.3)
Swelling			
Any (>5 mm)	13/ 149 (8.7) (4.7, 14.5)	25/ 243 (10.3) (6.8, 14.8)	38/ 392 (9.7) (7.0, 13.1)
Mild (>5-<25 mm)	6/ 149 (4.0) (1.5, 8.6)	17/ 243 (7.0) (4.1, 11.0)	23/ 392 (5.9) (3.8, 8.7)
Moderate (25-50 mm)	6/ 149 (4.0) (1.5, 8.6)	6/ 243 (2.5) (0.9, 5.3)	12/ 392 (3.1) (1.6, 5.3)
Severe (>50 mm)	1/ 149 (0.7) (0.0, 3.7)	2/ 243 (0.8) (0.1, 2.9)	3/ 392 (0.8) (0.2, 2.2)
Tenderness*			
Any	83/ 150 (55.3) (47.0, 63.4)	138/ 245 (56.3) (49.9, 62.6)	221/ 395 (55.9) (50.9, 60.9)
Mild	62/ 150 (41.3) (33.4, 49.7)	93/ 245 (38.0) (31.9, 44.4)	155/ 395 (39.2) (34.4, 44.2)
Moderate	15/ 150 (10.0) (5.7, 16.0)	38/ 245 (15.5) (11.2, 20.7)	53/ 395 (13.4) (10.2, 17.2)
Severe	6/ 150 (4.0) (1.5, 8.5)	7/ 245 (2.9) (1.2, 5.8)	13/ 395 (3.3) (1.8, 5.6)
Change in Limb Circumference			
Any (>5 mm)	50/ 149 (33.6) (26.0, 41.7)	83/ 240 (34.6) (28.6, 41.0)	133/ 389 (34.2) (29.5, 39.1)
Mild (>5-<20 mm)	44/ 149 (29.5) (22.3, 37.5)	71/ 240 (29.6) (23.9, 35.8)	115/ 389 (29.6) (25.1, 34.4)
Moderate (20-40 mm)	6/ 149 (4.0) (1.5, 8.6)	10/ 240 (4.2) (2.0, 7.5)	16/ 389 (4.1) (2.4, 6.6)
Severe (>40 mm)	0/ 149 (0.0) (0.0, 2.4)	2/ 240 (0.8) (0.1, 3.0)	2/ 389 (0.5) (0.1, 1.8)

Each subject is counted once and classified according to the highest recorded severity score; 'n' is the number of subjects with the indicated reaction and 'N' is the number of subjects with available data from the Safety Population.
*Mild = subject whimpers when site is touched, no crying; Moderate = subject cries when site is touched; Severe = subject cries when leg or arm is moved.
Source: p3t11.pdf, page 158

Table 6. Number (percentage) of subjects with solicited systemic reactions 0-7 days after dose 4 Pentacel, by participation in Study P3T11, Pentacel primed subjects from Study P3T06, safety population.

Reaction/Severity	Enrolled in Study P3T11 n/N % (95% CI)	Not Enrolled in Study P3T11 n/N % (95% CI)	Total
Fever*			
>=38.0 °C	31/ 148 (20.9) (14.7, 28.4)	40/ 241 (16.6) (12.1, 21.9)	71/ 389 (18.3) (14.5, 22.5)
>=38.0-<=38.5 °C	18/ 148 (12.2) (7.4, 18.5)	25/ 241 (10.4) (6.8, 14.9)	43/ 389 (11.1) (8.1, 14.6)
>38.5 °C-<=39.5 °C	12/ 148 (8.1) (4.3, 13.7)	13/ 241 (5.4) (2.9, 9.0)	25/ 389 (6.4) (4.2, 9.3)
>39.5 °C	1/ 148 (0.7) (0.0, 3.7)	2/ 241 (0.8) (0.1, 3.0)	3/ 389 (0.8) (0.2, 2.2)
Fussiness†			
Any	93/ 151 (61.6) (53.3, 69.4)	134/ 246 (54.5) (48.0, 60.8)	227/ 397 (57.2) (52.1, 62.1)
Mild	51/ 151 (33.8) (26.3, 41.9)	74/ 246 (30.1) (24.4, 36.2)	125/ 397 (31.5) (26.9, 36.3)
Moderate	30/ 151 (19.9) (13.8, 27.1)	49/ 246 (19.9) (15.1, 25.5)	79/ 397 (19.9) (16.1, 24.2)
Severe	12/ 151 (7.9) (4.2, 13.5)	11/ 246 (4.5) (2.3, 7.9)	23/ 397 (5.8) (3.7, 8.6)
Inconsolable Crying†			
Any	63/ 151 (41.7) (33.8, 50.0)	92/ 246 (37.4) (31.3, 43.8)	155/ 397 (39.0) (34.2, 44.0)
Mild	42/ 151 (27.8) (20.8, 35.7)	63/ 246 (25.6) (20.3, 31.5)	105/ 397 (26.4) (22.2, 31.1)
Moderate	19/ 151 (12.6) (7.7, 19.0)	22/ 246 (8.9) (5.7, 13.2)	41/ 397 (10.3) (7.5, 13.7)
Severe	2/ 151 (1.3) (0.2, 4.7)	7/ 246 (2.8) (1.2, 5.8)	9/ 397 (2.3) (1.0, 4.3)
Decreased Activity§			
Any	45/ 151 (29.8) (22.6, 37.8)	59/ 246 (24.0) (18.8, 29.8)	104/ 397 (26.2) (21.9, 30.8)
Mild	22/ 151 (14.6) (9.4, 21.2)	35/ 246 (14.2) (10.1, 19.2)	57/ 397 (14.4) (11.1, 18.2)
Moderate	18/ 151 (11.9) (7.2, 18.2)	18/ 246 (7.3) (4.4, 11.3)	36/ 397 (9.1) (6.4, 12.3)
Severe	5/ 151 (3.3) (1.1, 7.6)	6/ 246 (2.4) (0.9, 5.2)	11/ 397 (2.8) (1.4, 4.9)

Each subject is counted once and classified according to the highest recorded severity score; 'n' is the number of subjects with the indicated reaction and 'N' is the number of subjects with available data from the Safety Population.
*Fever is based upon actual temperatures recorded with no adjustments to the measurements for route.
†Mild = <1hour; Moderate = 1-3 hours; Severe = >3 hours.
§Mild = Usual daily activity is not affected; Moderate = Interferes with and limits usual daily activity; Severe = Disabling, not interested in usual daily activity.
Source: p3t11.pdf, page 163

6.8.2 Safety Outcomes

6.8.2.1 Immediate Reactions

No subject in Study P3T11 experienced hives, difficulty breathing, or anaphylaxis during the immediate 30 minute post-vaccination period.

6.8.2.2 Antipyretic Use

Among DAPTACEL primed subjects, within 3 days after vaccination in Study P3T11, antipyretics were used by 24.6% (120/487) of subjects. Among Pentacel primed subjects, within 3 days after vaccination in Study P3T11, antipyretics were used by 18.5% (30/162) of subjects.

6.8.2.3 Solicited Local Reactions

Approximately 70-75% of subjects reported at least one solicited local reaction within 0-3 days following DAPTACEL in Study P3T11. Table 7 presents the incidence and severity of the solicited local reactions that occurred within 3 days following each DAPTACEL or Pentacel vaccination for DAPTACEL and Pentacel primed subjects who participated in Study P3T11. Data on local reactions occurring between 0-7 days post-vaccination (not shown in this review), along with the data in Table 7, indicated that for nearly all solicited local reactions, the onset was within 0-3 days post-vaccination.

Table 7. Number (percentage) of subjects with solicited local reactions within 0-3 days after each dose of DAPTACEL or Pentacel, DAPTACEL and Pentacel primed subjects who participated in Study P3T11, safety population

	DAPTACEL for Doses 1-5					Pentacel for Doses 1-4 and DAPTACEL for Dose 5				
DTaP Dose Number*	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
	N=484	N=480	N=476	N=448-456	N=478-481	N=158-159	N=161	N=157	N=146-150	N=159-162
Reaction/Severity	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Redness at Injection Site										
>5 mm	32 (6.6)	30 (6.3)	37 (7.8)	79 (17.4)	172 (35.8)	9 (5.7)	12 (7.5)	14 (8.9)	24 (16.2)	38 (23.5)
>5-<25 mm	28 (5.8)	29 (6.0)	25 (5.3)	39 (8.6)	46 (9.6)	5 (3.1)	9 (5.6)	10 (6.4)	11 (7.4)	11 (6.8)
25-50 mm	3 (0.6)	1 (0.2)	12 (2.5)	28 (6.2)	50 (10.4)	4 (2.5)	3 (1.9)	4 (2.5)	12 (8.1)	12 (7.4)
>50 mm	1 (0.2)	0 (0.0)	0 (0.0)	12 (2.6)	76 (15.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	15 (9.3)
Swelling at Injection Site										
>5 mm	16 (3.3)	14 (2.9)	23 (4.8)	50 (11.0)	115 (23.9)	10 (6.3)	12 (7.5)	10 (6.4)	13 (8.8)	22 (13.6)
>5-<25 mm	8 (1.7)	11 (2.3)	17 (3.6)	31 (6.8)	50 (10.4)	5 (3.1)	7 (4.3)	5 (3.2)	6 (4.1)	6 (3.7)
25-50 mm	6 (1.2)	3 (0.6)	5 (1.1)	13 (2.9)	28 (5.8)	5 (3.1)	5 (3.1)	5 (3.2)	6 (4.1)	14 (8.6)
>50 mm	2 (0.4)	0 (0.0)	1 (0.2)	6 (1.3)	37 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.2)
Tenderness at Injection Site†										
Any	229 (47.3)	185 (38.5)	183 (38.4)	215 (47.1)	296 (61.5)	70 (44.3)	62 (38.5)	72 (45.9)	83 (55.3)	89 (54.9)
Mild	137 (28.3)	133 (27.7)	124 (26.1)	153 (33.6)	234 (48.6)	43 (27.2)	9 (30.4)	54 (34.4)	62 (41.3)	74 (45.7)
Moderate	73 (15.1)	45 (9.4)	51 (10.7)	50 (11.0)	54 (11.2)	23 (14.6)	11 (6.8)	16 (10.2)	15 (10.0)	15 (9.3)
Severe	19 (3.9)	7 (1.5)	8 (1.7)	12 (2.6)	8 (1.7)	4 (2.5)	2 (1.2)	2 (1.3)	6 (4.0)	0 (0.0)
Increase in Arm Circumference‡										
>5 mm	NM	NM	NM	133 (29.7)	183 (38.3)	NM	NM	NM	50 (34.2)	51 32.1)
>5-<20 mm	NM	NM	NM	104 (23.2)	109 (22.8)	NM	NM	NM	44 (30.1)	37 (23.3)
20-40 mm	NM	NM	NM	28 (6.3)	67 (14.0)	NM	NM	NM	6 (4.1)	14 (8.8)
>40 mm	NM	NM	NM	1 (0.2)	7 (1.5)	NM	NM	NM	0 (0.0)	0 (0.0)
Interference with Normal Activity of the Arm§										
Any	NM	NM	NM	NM	98 (20.4)	NM	NM	NM	NM	20 (12.3)
Mild	NM	NM	NM	NM	69 (14.3)	NM	NM	NM	NM	17 (10.5)
Moderate	NM	NM	NM	NM	27 (5.6)	NM	NM	NM	NM	3 (1.9)
Severe	NM	NM	NM	NM	2 (0.4)	NM	NM	NM	NM	0 (0.0)

*Doses 1-4 of DAPTACEL or Pentacel were administered in Study P3T06. In all subjects, the fifth DTaP dose was with DAPTACEL, administered in Study P3T11.

†Doses 1-4: Mild = subject whimpers when site is touched, no crying; Moderate = subject cries when site is touched; Severe = subject cries when leg or arm is moved. Dose 5: Mild = Noticeable, but did not interfere with activities; Moderate = Interfered with activities, but did not require medical care or absenteeism; Severe = Incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.

‡The circumference of the DAPTACEL or Pentacel injected arm at the level of the axilla was monitored following the fourth and fifth doses. Increase in arm circumference was calculated by subtracting the baseline circumference pre-vaccination (Day 0) from the circumference post-vaccination.
§Mild = Decreased movement of arm; Moderate = Decreased use of arm, but did not require medical care or absenteeism; Severe = Incapacitating, refusal to move arm, may have/or required medical care or absenteeism.
For each dose, each subject is counted once and is classified according to the highest recorded severity score; 'n' is the number of subjects with the indicated reaction and 'N' is the total number of subjects who received the indicated dose with available data from the Safety Population.
NM = Not monitored
DAPTACEL primed subjects 007-0008 and 014-0018 received Pentacel at Dose 4 and are not summarized at this dose.
Source: p3t11.pdf, pages 50, 51, 177, and 178.

In Study P3T11, for most subjects with injection site redness >50 mm within 0-3 days following receipt of DAPTACEL, the maximum reported size of the reaction was ≤100 mm. Nine DAPTACEL primed subjects (1.9%) and no Pentacel primed subjects reported injection site redness >100 mm within 0-3 days following DAPTACEL in Study P3T11. In Study P3T11, for most subjects with injection site swelling >50 mm within 0-3 days following receipt of DAPTACEL, the maximum reported size of the reaction was ≤100 mm. Three DAPTACEL-primed subjects (0.6%) and no Pentacel primed subjects reported injection site swelling >100 mm within 0-3 days following DAPTACEL in Study P3T11. There were no reports of injection site redness or swelling >150 mm (source: BLA STN# 103666/5158, Amendment 4, page 7).

Of the 7 subjects (all DAPTACEL primed) who reported >40 mm increase in circumference of the DAPTACEL injected arm in Study P3T11, the maximum increase from baseline measurement ranged from 45-80 mm, corresponding to increases of 23-44%. Four of these subjects also had severe redness and 1 had severe injection site swelling; none reported functional impairment of the vaccinated arm.

Among both DAPTACEL primed and Pentacel primed subjects, no case of extensive or whole limb swelling was reported as an unsolicited adverse event within 7 days after vaccination in Study P3T11.

Among DAPTACEL primed subjects who reported local reactions post-dose 5 DAPTACEL in Study P3T11, the mean durations for reactions occurring within 7 days were 3.0 days for redness, 2.8 days for swelling, 2.2 days for tenderness, 3.9 days for increase in arm circumference, and 1.9 days for interference with normal activity of the arm. Among Pentacel primed subjects who reported local reactions following DAPTACEL in Study P3T11, the mean durations for reactions occurring within 7 days were 2.6 days for redness, 3.3 days for swelling, 2.2 days for tenderness, 3.6 days for increase in arm circumference, and 2.0 days for interference with normal activity of the arm.

Among DAPTACEL primed subjects, the following local reactions within 0-3 days post-vaccination were reported as unsolicited adverse events: 4 subjects (0.8%) with injection site erythema, 2 subjects (0.4%) with injection site warmth, and 1 subject (0.2%) each with injection site discoloration, mass, nodule, pruritis, swelling, and tenderness. Two of these events, one each of injection site erythema and discoloration were graded as severe in intensity. The others were considered either mild or moderate in intensity. Among Pentacel primed subjects, the following local reactions within 0-3 days post-vaccination were reported as unsolicited adverse events: 2 subjects (1.2%) with injection site erythema and 1 subject (0.6%) with injection site bruising. One Pentacel primed subject reported pain within 3 days post-vaccination as an unsolicited symptom, but the location of the pain was not specified. None of these events in the Pentacel primed subjects was considered severe.

6.8.2.4 Solicited Systemic Reactions

Table 8 presents the incidence and severity of solicited systemic reactions that occurred within 3 days of each DAPTACEL or Pentacel vaccination for DAPTACEL and Pentacel primed subjects who participated in Study P3T11. Data on solicited systemic reactions occurring between 0-7 days post-vaccination (not shown in this review), along with the data in Table 8, indicated that for most solicited systemic reactions, the onset was within 0-3 days post-vaccination.

Table 8. Number (percentage) of subjects with selected solicited systemic reactions occurring between 0-3 days after each dose of DAPTACEL or Pentacel, DAPTACEL and Pentacel primed subjects, safety population

	DAPTACEL for Doses 1-5					Pentacel for Doses 1-4 and DAPTACEL for Dose 5				
DTaP Dose Number*	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
	N=481-485	N=478-481	N=474-476	N=453-458	N=473-481	N=159	N=161	N=156-157	N=148-151	N=156-162
Reaction/Severity	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Fever†										
>=38.0 °C	45 (9.4)	74 (15.5)	71 (15.0)	44 (9.7)	29 (6.1)	8 (5.0)	19 (11.8)	28 (17.9)	21 (14.2)	8 (5.1)
>=38.0-<=38.5 °C	42 (8.7)	57 (11.9)	53 (11.2)	26 (5.7)	18 (3.8)	7 (4.4)	16 (9.9)	21 (13.5)	12 (8.1)	5 (3.2)
>38.5 °C-<=39.5 °C	3 (0.6)	15 (3.1)	17 (3.6)	14 (3.1)	10 (2.1)	1 (0.6)	3 (1.9)	4 (2.6)	9 (6.1)	2 (1.3)
>39.5 °C	0 (0.0)	2 (0.4)	1 (0.2)	4 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)	3 (1.9)	0 (0.0)	1 (0.6)
Fussiness/Irritability‡										
Any	364 (75.1)	344 (71.5)	314 (66.0)	258 (56.3)	168 (34.9)	124 (78.0)	123 (76.4)	109 (69.4)	89 (58.9)	43 (26.5)
Mild	206 (42.5)	196 (40.7)	195 (41.0)	165 (36.0)	130 (27.0)	76 (47.8)	74 (46.0)	65 (41.4)	47 (31.1)	34 (21.0)
Moderate	131 (27.0)	121 (25.2)	95 (20.0)	79 (17.2)	36 (7.5)	44 (27.7)	42 (26.1)	38 (24.2)	32 (21.2)	9 (5.6)
Severe	27 (5.6)	27 (5.6)	24 (5.0)	14 (3.1)	2 (0.4)	4 (2.5)	7 (4.3)	6 (3.8)	10 (6.6)	0 (0.0)
Inconsolable Crying§										
Any	281 (57.9)	245 (50.9)	212 (44.5)	174 (38.0)	68 (14.1)	86 (54.1)	82 (50.9)	83 (52.9)	58 (38.4)	17 (10.5)
Mild	211 (43.5)	160 (33.3)	159 (33.4)	127 (27.7)	49 (10.2)	60 (37.7)	62 (38.5)	60 (38.2)	38 (25.2)	12 (7.4)
Moderate	59 (12.2)	67(13.9)	45 (9.5)	40 (8.7)	17 (3.5)	24 (15.1)	19 (11.8)	23 (14.6)	18 (11.9)	5 (3.1)
Severe	11 (2.3)	18 (3.7)	8 (1.7)	7 (1.5)	2 (0.4)	2 (1.3)	1 (0.6)	0 (0.0)	2 (1.3)	0 (0.0)
Decreased Activity/Lethargy**										
Any	235 (48.5)	179 (37.2)	154 (32.4)	122 (26.6)	101 (21.0)	68 (42.8)	52 (32.3)	57 (36.3)	41 (27.2)	25 (15.4)
Mild	125 (25.8)	108 (22.5)	92 (19.3)	72 (15.7)	69 (14.3)	37 (23.3)	32 (19.9)	36 (22.9)	24 (15.9)	20 (12.3)
Moderate	106 (21.9)	66 (13.7)	58 (12.2)	45 (9.8)	28 (5.8)	28 (17.6)	18 (11.2)	21 (13.4)	12 (7.9)	4 (2.5)
Severe	4 (0.8)	5 (1.0)	4 (0.8)	5 (1.1)	4 (0.8)	3 (1.9)	2 (1.2)	0 (0.0)	5 (3.3)	1 (0.6)

*Doses 1-4 of DAPTACEL or Pentacel were administered in Study P3T06. In all subjects, the fifth DTaP dose was with DAPTACEL, administered in Study P3T11.

†In Study P3T06, the protocol specified that temperatures be measured rectally. Considering all DAPTACEL and Pentacel primed subjects in Study P3T06, irrespective of participation in Study P3T11, for Doses 1-3, approximately half of temperatures were measured rectally, approximately 45% were measured axillary, and <5% were measured by other or unspecified routes; for Dose 4, approximately two-thirds of temperatures were measured axillary, approximately one-third were measured rectally and <5% were measured by other or unspecified routes. In Study P3T11, the protocol specified that temperatures be measured orally. In Study P3T11, approximately 90% of temperatures were measured orally and approximately 10% were measured axillary. Fever is based upon actual temperatures recorded with no adjustments to the measurements for route.

‡For Doses 1-4, Fussiness was solicited, using the following severity scale: Mild = <1hour; Moderate = 1-3 hours; Severe = >3 hours. For Dose 5, Irritability was solicited, using the following severity scale: Mild = Noticeable, but did not interfere with activities; Moderate = interfered with activities, but did not require medical care or absenteeism; Severe = Incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.

§Doses 1-4: Mild = <1 hour; Moderate = 1-3 hours; Severe = >3 hours. Dose 5: Mild = Noticeable, but did not interfere with activities; Moderate = Interfered with activities, but did not require medical care or absenteeism; Severe = Incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.
**For Doses 1-4, Decreased activity was solicited, using the following severity scale: Mild = Usual daily activity is not affected; Moderate = Interferes with and limits usual daily activity; Severe = Disabling, not interested in usual daily activity. For Dose 5, Decreased activity/Lethargy was solicited, using the following severity scale: Mild = Noticeable, but did not interfere with activities; Moderate = Interfered with activities, but did not require medical care or absenteeism; Severe = Incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.
Source: p3t11.pdf, pages 51, 216, 217, 790, DAPTACEL package insert approved November 2006; Pentacel BLA STN ------- p3t06si.pdf page 493 and p3t06sii.pdf page 117.

Among DAPTACEL primed subjects who reported solicited systemic reactions post-dose 5 DAPTACEL in Study P3T11, the mean durations for reactions occurring within 7 days were 2.1 days for fever, 1.8 days for irritability, 1.5 days for crying, and 1.6 days for lethargy. Among Pentacel-primed subjects who reported solicited systemic reactions following DAPTACEL in Study P3T11, the mean durations for reactions occurring within 7 days were 2.2 days for fever, 2.0 days for irritability, 1.5 days for crying, and 1.6 days for lethargy.

6.8.2.5 Unsolicited Adverse Events, Including Serious Adverse Events

In Study P3T11, within 30 days post-vaccination, 171 (26.3%) subjects overall (DAPTACEL primed and Pentacel primed pooled), reported at least one unsolicited adverse event. During this period, the most frequently reported unsolicited events were cough (4.2% of subjects), upper respiratory tract infection not otherwise specified (3.4% of subjects), and otitis media not otherwise specified (1.8% of subjects).

A total of 8 subjects experienced at least one serious adverse event within 0 to 180 days following administration of DAPTACEL in Study P3T11 (Table 9). During this period, no deaths were reported.

Table 9. Study P3T11 Serious adverse events occurring between 0-180 days after DAPTACEL, safety population

DTaP Vaccine Received in Study P3T06	Subject	Days Since Vaccination in Study P3T11	Preferred Term	Literal Term
Pentacel	005-00020	109	Gastroenteritis NOS	Gastroenteritis
		109	Dehydration	Dehydration
	018-00001	171	Supraventricular tachycardia	Paroxysmal supraventricular tachycardia
		177	Gastroenteritis NOS	Gastroenteritis
	024-00029	2	Thrombocytopenic purpura	Probable immune thrombocytopenic purpura
DAPTACEL	003-00025	89	Asthma NOS	Asthma acute exacerbation
	003-00104	146	Otitis media NOS	Bilateral otitis media
		146	Pneumonia respiratory syncytial viral	RSV-pneumonitis
	020-00028	10	Bronchospasm NOS	Reactive airway disease
		10	Hypoxia	Hypoxia
		152	Head injury	Head injury
		152	Skull fracture NOS	Skull fracture
	023-00002	97	Asthma NOS	Acute asthma exacerbation
	024-00002	122	Staring	Staring episodes

Source: p3t11.pdf, pages 100-101.

Clinical case narratives are provided below for the two subjects who reported a serious adverse event within 10 days post-vaccination.

> Subject 020-00028, a 4 year-old female who previously received 4 doses of DAPTACEL in Study P3T06, received DAPTACEL, IPOL and MMR_{II} in Study P3T11. She was hospitalized one day for hypoxia and reactive airway disease, with onset of symptoms nine days post-vaccination.
>
> Subject 024-00029, a male subject who previously received 4 doses of Pentacel in Study P3T06, received DAPTACEL and MMR_{II} in Study P3T11. For approximately one month prior to

vaccination, the subject had an upper respiratory infection. He experienced bruising 19 days prior to vaccination. On day 2 post-vaccination, ecchymotic areas on the knees and elbows were noted, and his platelet count was 103,000 (normal range: 136,000 - 400,000). Serological testing was consistent with past Epstein-Barr virus infection. The subject was thought to have Immune Thrombocytopenic Purpura as a result of recent Epstein-Barr virus infection. Platelet counts on days 6, 14, 27, 74, and 98 post-vaccination, were 115,000, 125,000, 145,000, 95,000 and 87,000, respectively. The event was ongoing at 9 months post vaccination.

In Study P3T11, there were no reports of hypotonic hyporesponsive episode or seizures.

6.8.3 Immunogenicity Outcomes

As indicated previously in Sections 4.2 and 5.2, CBER has not required immunogenicity data to support approval of booster doses of DTaP vaccines following an approved primary series with the same DTaP vaccine. In Study P3T11, there were no pre-specified criteria to assess the acceptability of the immune response to a fifth dose of DAPTACEL or to a fourth dose of IPV. ----------.

4 Pages determined not to be releasable

6.9 Comments and Conclusions

6.9.1 Study Design and Population

Study P3T11 provides uncontrolled data on the occurrence of relatively common local and systemic adverse events following DAPTACEL administered in children 4-6 years of age who previously received four doses of either DAPTACEL or Pentacel. In view of the sample size of 649 subjects, the study was not sufficiently powered to reliably assess relatively uncommon, serious adverse events following DAPTACEL. In previous clinical studies of DAPTACEL, serious adverse events were evaluated in approximately 5,000 children who received three or four consecutive doses of DAPTACEL.[3]

Safety data on administration of DAPTACEL at 4-6 years of age were provided on 487 subjects previously primed with DAPTACEL and 162 subjects previously primed with Pentacel. Although Pentacel is not licensed in the U.S., the safety data on Pentacel primed subjects are considered supportive for evaluation of a fifth consecutive dose of DAPTACEL.

The study population for Study P3T11 was a non-random subset of subjects (39%) who previously received four doses of DAPTACEL or Pentacel in Study P3T06. Study P3T11 subjects appeared to be representative of all subjects who participated in Study P3T06 with regard to post-dose 4 solicited local and systemic adverse events.

Subjects in Study P3T11 received DAPTACEL concomitantly with the second dose of MMR vaccine. Those subjects who previously had been vaccinated with four doses of DAPTACEL also received IPOL concomitantly with the fifth dose of DAPTACEL. Study P3T11 was initiated prior to the ACIP's recommendation to administer a second dose of varicella vaccine at 4-6 years of age. Thus, subjects did not receive varicella vaccine in Study P3T11. However, in Study P3T06, which previously was reviewed under DAPTACEL BLA Supplement 103666/5071, a subset of 420 subjects received the fourth dose of DAPTACEL concomitantly with the first dose of VARIVAX (Merck & Co., Inc.). Safety data on the fifth dose of DAPTACEL administered concomitantly with the second dose of varicella vaccine will be available from an ongoing study, Study Td517 "Safety and Immunogenicity of ADACEL® (TdaP) Compared to DAPTACEL® as Fifth Dose Booster in Children 4 to 6 Years of Age", being conducted under the ADACEL IND. In Study Td517, 500 children previously vaccinated with four doses of either DAPTACEL or Pentacel are expected to receive DAPTACEL concomitantly with MMR and varicella vaccine at 4-6 years of age. Data from this study will be reviewed under the ADACEL IND.

6.9.2 Safety

Overall, approximately 70-75% of subjects in Study P3T11 reported at least one solicited local reaction within 0-3 days following DAPTACEL administered as the fifth dose of DTaP at 4-6 years of age. Historically, the fifth consecutive dose of DTaP vaccines has been associated with higher rates and increased severity of local reactions compared to previous doses.[1,2] Findings from Study P3T11 are consistent with this observation. Rates of local redness and swelling of any severity following DAPTACEL administered as a fifth dose of DTaP in children previously primed with either DAPTACEL or Pentacel appeared to be higher than following earlier doses of either DAPTACEL or Pentacel (Table 7). Also of note is that rates of injection site redness >50 mm and injection site swelling >50 mm appeared to be higher following DAPTACEL administered at 4-6 years of age compared to previous doses of either DAPTACEL or Pentacel (Table 7). Rates of injection site tenderness and increased arm circumference also tended to be higher following the fifth dose of DAPTACEL compared to the fourth dose in DAPTACEL primed subjects (Table 7). In Pentacel primed subjects, the rates of injection site tenderness and increased arm circumference were similar following DAPTACEL administered at 4-6 years of age and the fourth dose of Pentacel administered at 15-17 months of age (Table 7).

Solicited systemic adverse events following DAPTACEL in Study P3T11 occurred at a lower frequency than following Doses 1-4 of DAPTACEL or Pentacel in Study P3T06 (Table 8). The most frequently occurring solicited systemic adverse event within 0-3 days after receipt of DAPTACEL in Study P3T11 was irritability, reported in approximately 25-35% of subjects. In Study P3T11, approximately 5% of subjects reported fever $\geq$38.0^{o}C within 0-3 days following DAPTACEL, with <0.5% of subjects reporting fever >39.5^{o}C.

There were two reports of serious adverse events within 30 days following DAPTACEL in Study P3T11—one case of hypoxia and reactive airways disease with onset of symptoms 9 days post-vaccination and one case of immune thrombocytopenic purpura in a subject who had onset of bruising 19 days prior to vaccination. The nature and timing of these events do not suggest a causal relationship with vaccination.

6.9.3 Immunogenicity

As discussed in Section 4.2, for DTaP vaccines that have been approved for a primary series, CBER has not required an evaluation of immunogenicity to support approval of booster doses following a primary series with the same DTaP vaccine. ----------
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In the context of concomitant vaccine administration, CBER has not required an evaluation of the immune responses to the second dose of MMR and varicella vaccines as most subjects are expected to be seropositive/seroprotected prior to vaccination. Data on the immune response to the first dose of MMR and varicella vaccines administered concomitantly with the fourth dose of DAPTACEL are included in the DAPTACEL package insert.[3]

7. Partial Waiver of Pediatric Studies

The applicant has requested a waiver of the requirement to submit pediatric studies of DAPTACEL in infants from birth to 6 weeks of age and in children and adolescents 7-16 years of age. Based on the justification provided below, I concur that waivers of pediatric studies of DAPTACEL in these age groups should be granted. In the 2/5/08 meeting of FDA's Pediatric Review Committee, the committee also concurred with granting waivers for studies of DAPTACEL in these age groups.

7.1 Infants from Birth to 6 Weeks of Age

For infants from birth to 6 weeks of age, the justification for waiver of studies with DAPTACEL is based on the following sections of the Pediatric Research Equity Act of 2007:

Section 505B(a)(4)(B)(i): necessary studies are impossible or highly impracticable.

Section 505B(a)(4)(B)(iii): the drug or biological product—(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is not likely to be used by a substantial number of pediatric patients in that age group.

Necessary studies are impossible or highly impracticable
It would be difficult to enroll sufficient numbers of subjects from birth to 6 weeks of age in studies of DAPTACEL and inappropriate to require such studies because of:

- the lack of apparent benefit of administration of diphtheria toxoid and tetanus toxoid to U.S. infants <6 weeks of age, compared with vaccination beginning at 6 weeks of age;
- the potential for immune suppression to subsequent vaccination that may be associated with early-life vaccination;
- the potential for clinically significant fever and other adverse events that may be associated with vaccination of vulnerable neonates.

With the exception of hepatitis B vaccine, which is routinely administered shortly after birth, in part, to prevent unrecognized perinatal transmission of hepatitis B virus, the infant immunization program in the U.S. is initiated at a minimum of 6 weeks of age. In general, limitations of the neonatal immune response (e.g., weak and short-lived antibody response and inhibitory influence of maternal antibodies) have been significant barriers to effective immunization earlier in life.

Among the diseases targeted for prevention by DAPTACEL, only pertussis occurs in U.S. infants who are too young to be protected as a result of vaccination beginning at 6 weeks of age. With regard to diphtheria and tetanus, not only is there no apparent need for earlier vaccination, clinical data from one published study suggest that administration of Diphtheria and Tetanus Toxoids Adsorbed For Pediatric Use (DT) to newborn infants may be associated with suppression of antibody responses to subsequently administered diphtheria toxoid and *Haemophilus influenzae* type b conjugate vaccines.[4]

As with all preventive vaccines, a high standard of safety would be expected for vaccines administered to healthy neonates. Moreover, the vulnerability of the neonate poses unique safety considerations for clinical studies of preventive vaccines. For example, post-vaccination fever assumes greater clinical significance in neonates than in older infants or children because of the high risk for serious bacterial infection and the difficulty in predicting the presence of invasive disease by physical exam and laboratory testing in the neonatal period. Hospitalization, diagnostic evaluation including cerebrospinal fluid studies, and administration of intravenous antibiotics represent the standard of care in the U.S. for febrile neonates. Administration of DAPTACEL in infants from birth to 6 weeks of age poses at least a theoretical concern for excess fever due to vaccination. In a U.S. study, 9-16% of older infants had fever $\geq$38.0^{o}C within 0-3 days following receipt of DAPTACEL.[3]

DAPTACEL does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a substantial number of infants from birth to 6 weeks of age
For the prevention of diphtheria and tetanus, DAPTACEL administered to U.S. infants from birth to 6 weeks of age does not represent a meaningful therapeutic benefit over administration of DAPTACEL or other DTaP-containing vaccines according to the currently recommended schedule which begins at a minimum age of 6 weeks. In view of the potential risks of neonatal vaccination and the lack of added benefit to earlier vaccination against diphtheria and tetanus, DAPTACEL is not likely to be used by a substantial number of U.S. infants from birth to 6 weeks of age.

7.2 Children and Adolescents 7-16 Years of Age
The justification for waiver of studies of DAPTACEL in children and adolescents 7-16 years of age is based on the following sections of the Pediatric Research Equity Act of 2007:

Section 505B(a)(4)(B)(i): necessary studies are impossible or highly impracticable.

Section 505B(a)(4)(B)(iii): the drug or biological product—(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is not likely to be used by a substantial number of pediatric patients in that age group.

Necessary studies are impossible or highly impracticable
Because of the following considerations, it would not be feasible to conduct studies of DAPTACEL in children and adolescents 7-16 years of age, and inappropriate to require such studies.

- A fifth dose of DTaP, routinely administered prior to school entry at age 4-6 years, completes the routinely recommended series for this vaccine.
- A single dose of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) is routinely recommended at 11-12 years of age. For adolescents 11-16 years of age, two Tdap vaccines, ADACEL and BOOSTRIX, are licensed and distributed in the U.S. BOOSTRIX is also approved for use in children 10 years of age. Both available Tdap vaccines were specifically formulated to contain lower amounts of diphtheria toxoid than DTaP vaccines to reduce the potential for reactogenicity that may be associated with booster vaccination.
- With regard to the age group 7-9 years, for which there are no licensed pertussis vaccines in the U.S., a very small number of children, geographically dispersed, would be expected to need vaccination against diphtheria, tetanus, and pertussis. Furthermore, three Td vaccines (Tetanus and Diphtheria Toxoids Adsorbed for Adult Use) are licensed for use in children 7-9 years of age, although few children in this age group are in need of these vaccines. Thus, studies to evaluate DAPTACEL in children 7-9 years of age would be highly impracticable.

DAPTACEL does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a substantial number of children and adolescents 7-16 years of age

- For children and adolescents 10-16 years of age, DAPTACEL does not represent a meaningful therapeutic benefit over Tdap. There are also three Td vaccines approved for use in children and adolescents 7-16 years of age. Vaccination with DAPTACEL at 7-9 years of age (no available pertussis vaccine for this age group) does not represent a meaningful therapeutic benefit over the current schedule of routine DTaP vaccination at 4-6 years of age and routine Tdap vaccination at 11-12 years of age.
- Given the availability of Tdap vaccines that have a lower amount of diphtheria toxoid relative to DAPTACEL, it is unlikely that DAPTACEL would be used by a substantial number of children and adolescents 7-16 years of age. With regard to the age group 7-9 years, for which Tdap vaccines are not approved, very few U.S. children would be expected to need vaccination against the three diseases targeted by DAPTACEL. If there was a need to study a preventive vaccine for diphtheria, tetanus, and pertussis in this age group, Tdap vaccines would be preferable over DAPTACEL because of their lower diphtheria toxoid content.

8. Recommendations

8.1 Approval Recommendation

The safety data provided in this Supplement, combined with previous clinical experience with DAPTACEL administered to infants and children ages 6 weeks through 20 months of age, support a recommendation for approval of a fifth dose of DAPTACEL in children 4-6 years of age who have previously received four doses of DAPTACEL. As discussed in Section 4.2, in considering the approvability of booster doses of DTaP vaccines following an approved primary series with the same vaccine, CBER has not required an

evaluation of the immune response to the booster doses. The data provided in this Supplement are not sufficient to support use of DAPTACEL following previous doses of other manufacturers' DTaP vaccines.

8.2 Post-marketing Actions
No new post-marketing actions are recommended.

8.3 Partial Waiver of Pediatric Studies
See Section 7 for recommendations for waiver of studies of DAPTACEL in pediatric populations from birth to 6 weeks of age and 7-16 years of age.

8.4 Labeling
The package insert submitted by the applicant is in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006. Specific comments on the revised labeling (not included in this review) have been conveyed to the applicant.

9 References

1. Tripedia package insert December 2003.

2. INFANRIX package insert July 2003.

3. DAPTACEL package insert November 2006.

4. Lieberman JM, Greenberg DP, Wong VK, et. al. Effect of neonatal immunization with diphtheria and tetanus toxoids on antibody responses to *Haemophilus influenzae* type b conjugate vaccines. J Pediatr 1995;126:198-205.