Summary Basis for Regulatory Action

Date: March 24, 2015

From: LCDR Matthew Steele, PhD

BLA/ STN#: 125525/0

Applicant Name: Sanofi-Pasteur Ltd

Date of Submission: March 24, 2014

PDUFA Goal Date: March 24, 2015

Established Name: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine

Proprietary Name: Quadracel

Indication: Prevention of diphtheria, tetanus, pertussis and poliomyelitis in children ages 4 through 6 years. A single dose of Quadracel is approved for use in children 4 through 6 years of age as a fifth dose in the diphtheria, tetanus, pertussis vaccination (DTaP) series, and as a fourth or fifth dose in the inactivated poliovirus vaccination (IPV) series, in children who have received 4 doses of Pentacel® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus and Haemophilus b conjugate (Tetanus Toxoid Conjugate) Vaccine] and/or DAPTACEL® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed).

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Marion Gruber, PhD, Director, Office of Vaccines

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.

Material Reviewed/ Consulted	Reviewer Name
Clinical Review	Sarah Browne, MD
Clinical Assays Statistics Review	Zhong Gao, PhD
Statistical Review	Ghideon Solomon, PhD
CMC Review	Tod Merkel, PhD

	Tahir Malik, PhD James Keller, PhD Juan Arciniega, DSc
Epidemiology/Pharmacovigilance Review	Patricia Rohan, MD
Bioresearch Monitoring Review	Dennis Cato, BS
Facility / CMC Review	LCDR Donald Ertel, MS
Pertussis Clinical Serology Assays Review	Freyja Lynn, BS
Diphtheria/Tetanus Clinical Serology Assays Review	Leslie Wagner, BS
Advertising and Promotional Labeling Review	Sonny Saini, PharmD
Product Release Review	Karen Campbell, MS
RPM Memo	LCDR Matthew Steele, PhD
Quadracel Final Draft Package Insert	N/A

1. Introduction

On March 24, 2014, Sanofi Pasteur Limited (license #1726), submitted a Biologics License Application (BLA) for Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine [DTaP-IPV], with the proposed trade name, Quadracel. The proposed indication is prevention of diphtheria, tetanus, pertussis and poliomyelitis disease in children 4 through 6 years of age. Quadracel is intended for use as the fifth DTaP dose in children 4 through 6 years of age whose previous four DTaP doses have been with Pentacel [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine] and/or DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed). These three vaccines contain the same acellular pertussis antigens manufactured by Sanofi Pasteur Limited according to the same process. Quadracel is intended for the last dose in the IPV series, which is recommended for administration at age 4 through 6 years. At 4 through 6 years of age, children vaccinated according to the recommended immunization schedule in the U.S. will previously have received either three or four doses of IPV. Thus, Quadracel is intended for use as the fourth or fifth dose of IPV, completing the recommended IPV series.

The active ingredients include tetanus and diphtheria toxoids, acellular pertussis antigens (pertussis toxoid; filamentous haemagglutinin; fimbriae types 2 and 3; and pertactin) and inactivated poliovirus types 1, 2, and 3. The vaccine antigens are combined with aluminum phosphate, which acts as an adjuvant.

The manufacturing information for Quadracel is incorporated by cross-reference from the Applicant's approved Pentacel vaccine file submitted under STN 125145 (Originally submitted July 26, 2005). The final presentation for Pentacel vaccine consists of two vials. One vial contains diphtheria toxoid, tetanus toxoid acellular pertussis antigens, and Inactivated Poliovirus Vaccine (DTaP-IPV component) in suspension which is used to reconstitute the second vial of lyophilized *Haemophilus influenzae* type b capsular polysaccharide conjugated to tetanus toxoid. The Quadracel product contains the same components and is manufactured by the same process as the liquid DTaP-IPV component of Pentacel vaccine.

The applicant conducted two clinical studies: a phase 3 study evaluating safety and immunogenicity of Quadracel in children 4 through 6 years of age (M5I02) and a supportive phase 2 study providing additional safety data (Td508).

This document summarizes the data submitted to this BLA and supporting chemistry and manufacturing documentation from the previously approved Pentacel vaccine application which serve as the basis of the review committee's recommendation to approve Quadracel for the proposed indication.

Background

In the US, the recommended schedule for DTaP vaccines consists of five doses administered at 2, 4, 6, and 15-18 months of age and 4-6 years of age. The recommended schedule for IPV vaccines consists of four doses administered at 2, 4, and 6-18 months and 4-6 years of age. If four or more doses are administered before age 4 years, an additional dose should be administered at age 4-6 years.

For U.S.-licensed DTaP and DTaP-based combination vaccines, including DAPTACEL and Pentacel, the approved usage includes mixed sequences of vaccines from the same manufacturer. However, the use of mixed sequences of vaccines from different manufacturers for completion of the DTaP series is not approved.

Currently, at 4 through 6 years of age, children completing a DAPTACEL and/or Pentacel DTaP series and receiving their last dose of IPV would receive separately administered DAPTACEL and IPV. In these children, the licensure and availability of Quadracel will allow completion of the DTaP and IPV series with one injection instead of two.

Quadracel is identical to the DTaP-IPV component of Pentacel, and is manufactured under the same conditions. Sanofi Pasteur has provided a unique lot release protocol as part of this BLA submission, but otherwise incorporates by cross-reference the entirety of the approved Pentacel file to describe the manufacture of Quadracel.

Quadracel is currently licensed in several other countries including Canada and Mexico.

2. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Quadracel is manufactured in a manner identical to that of the DTaP-IPV component of Pentacel (DTaP-IPV/HiB), which is presented as two vials: one contains a lyophilized *H. influenzae* type b component and the other contains DTaP-IPV in a sterile suspension.

The applicant incorporated by cross-reference the entirety of the approved Pentacel file to support licensure of Quadracel, with the exception of the lot release protocol. CBER considered the information pertaining to manufacture, in-process testing and release specifications from the Pentacel file adequate to support approval of Quadracel.

Quadracel is presented as a sterile, white cloudy liquid in single use vials without preservatives. One dose consists of 0.5 mL for intramuscular administration. Table 1 summarizes the composition of each 0.5 mL dose of Quadracel.

Table 1: Composition of Each 0.5 mL Dose of Quadracel

Component	Amount
Diphtheria Toxoid	15 Lf
Tetanus Toxoid	5 Lf
Pertussis Toxoid (PTx)	20 µg
Filamentous Haemagglutinin (FHA)	20 µg
Pertactin (PRN)	3 µg
Fimbriae Types 2 and 3 (FIM)	5 µg
Inactivated Polio Type 1 (Mahoney)	40 D-antigen units
Inactivated Polio Type 2 (MEF-1)	8 D-antigen units
Inactivated Polio Type 3 (Saukett)	32 D-antigen units
Aluminum Phosphate (Adjuvant)	1.5 mg (0.33 mg as Aluminum)
2-phenoxyethanol (not a preservative)	0.6% v/v
Polysorbate 80	10 ppm

Additional excipients include Bovine Serum Albumin (BSA), formaldehyde, glutaraldehyde, neomycin, and polymyxin B.

Below is a brief overview of the manufacture of each Bulk Drug Substance.

Diphtheria Toxoid

(b) (4)

(b) (4)

(b) (4)

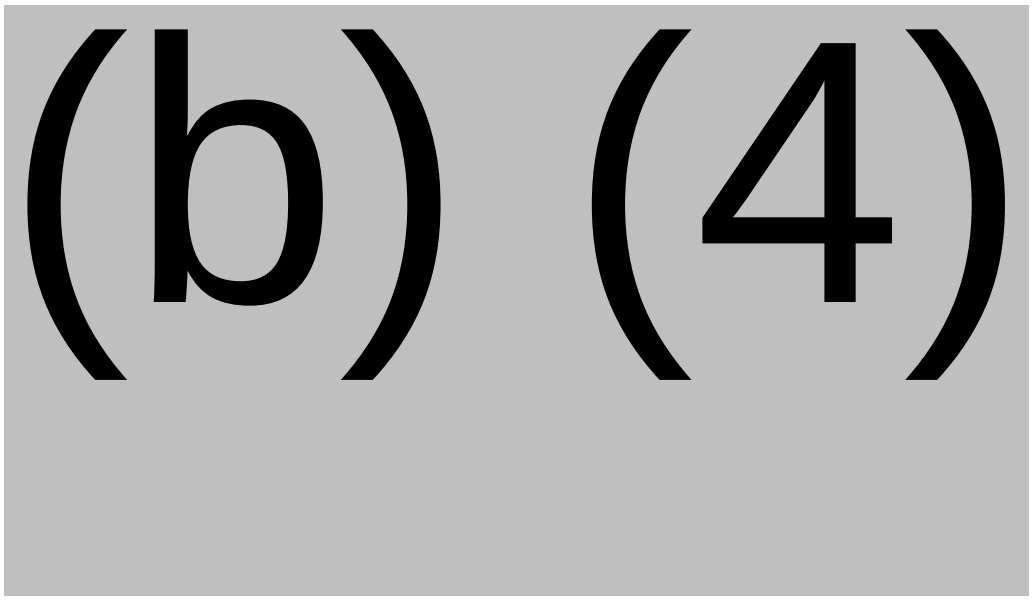
(b) (4)

Tetanus Toxoid Manufacture

(b) (4)

(b) (4)

(b) (4)



Final Drug Product

The adsorbed diphtheria, tetanus and acellular pertussis antigens are combined with aluminum phosphate, 2-phenoxyethanol and water for injection, into an intermediate concentrate. The trivalent poliovirus concentrate is added and the vaccine is diluted with water for injection containing polysorbate 80 (b) (4) to its final concentration. Quadracel is filled into single use vials, which are then stoppered with non-latex stoppers.

Table 9: Final Drug Product Release Specifications

Test	Specifications
Aluminum	(b) (4)
2-Phenoxyethanol	(b) (4)
(b) (4)	
Formaldehyde	(b) (4)
Polysorbate 80 (b) (4)	
Antigenicity Testing for the Diphtheria Component	≥ 2 units/mL Diphtheria antitoxin
Antigenicity Testing for the Tetanus Component	≥ 2 units/mL Tetanus antitoxin
Endotoxin	(b) (4)
Sterility	No growth
(b) (4)	
D-Antigen Content- (b) (4)	(b) (4)
(b) (4)	
Immunogenicity Acellular Pertussis (Mouse) (b) (4)	(b) (4)
Immunogenicity Acellular Pertussis (Mouse) (b) (4)	(b) (4)

b) CBER Lot Release

A review issue concerning lot release and mycoplasma testing of (b) (4) IPV lots arose and was resolved. Specifically, discrepancies were noted between the reporting of the results of the mycoplasma tests performed on each of the individual IPV (b) (4) in the lot release protocol submitted to the Quadracel file and the description of such tests contained in the cross-referenced Pentacel file. Currently, the licensed DTaP-IPV manufacturing process in the Pentacel file includes the use of (b) (4) tests for mycoplasma in the IPV (b) (4) lots (b) (4) .

It was determined during the review that the Applicant had made a change to these mycoplasma tests in order to bring them into conformity with (b) (4) standards. The applicant had thought that the change could be reported in the annual report due in 2015, and did not need to otherwise report the change in the Pentacel file. This change included dropping the number of tests from (b) (4) . However, while some IPV (b) (4) lots had been tested using this new mycoplasma testing method, none of these lots had been incorporated into any lot of Pentacel or the launch lots of Quadracel. As requested by CBER, the applicant amended the submitted lot release template to reflect the actual mycoplasma testing performed on IPV (b) (4) lots used in the manufacture of the existing Quadracel lots.

The lot release protocol templates were submitted to CBER for review and found to be acceptable after revisions. For post approval lot release, the applicant will submit a lot release protocol and samples of final bulk from each lot. Routine Lot Release is performed by reviewing the submitted Lot Release Protocol and by testing according to the lot release testing plan developed by CBER.

c) Facilities Review/Inspection

The facility involved in the manufacture of Quadracel is provided in the table below. The activities performed and the inspectional history of this facility is included in the table.

Table 10: Manufacturing Facility Information for Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
Manufacture, Labeling, and Testing of Drug Substance and Drug Product Sanofi Pasteur Limited 1755 Steeles Ave W Toronto, Canada	3002888623	208206623	Inspection waived	Team Biologics Sep 2013 VAI *See notes below*

Team Biologics performed a surveillance inspection of the Sanofi Pasteur Limited Toronto manufacturing facility from September 9 - 20, 2013. All Form FDA 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

The facility information and data provided in the BLA are sufficient and acceptable.

d) Environmental Assessment

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

e) Validation

All in-process and release assays were previously submitted to the Pentacel file. These assays are suitable for their intended usage.

3. Nonclinical Pharmacology/Toxicology

No nonclinical Pharmacology or Toxicology studies were required in order to support this application.

4. Clinical Pharmacology

The mechanism of protection conferred by immunization with the tetanus and diphtheria toxoids consists of the production of antibodies that have been scientifically established as correlating with protection.

There is no well-established serological correlate of protection for pertussis. The effectiveness of Quadracel against pertussis was based on a comparison of pertussis immune responses following Quadracel to those following DAPTACEL. Quadracel and DAPTACEL contain the same pertussis antigens manufactured by the same

process, although Quadracel contains twice as much PTx and four times as much FHA as DAPTACEL. The efficacy of the pertussis component of DAPTACEL previously was determined in clinical endpoint efficacy trials conducted in infants.

Neutralizing antibodies raised against the inactivated polioviruses confer protection by blocking cell invasion and promoting phagocytosis of the virus.

5. Clinical/ Statistical

a) Clinical Program

To support the licensure of Quadracel, the applicant submitted the results from two clinical trials: M5I02, which served as the clinical basis for licensure with regards to safety and immunogenicity, and Td508, which provided supportive safety data. The objective of the clinical development program was to evaluate the immunogenicity and safety of Quadracel in children 4 through 6 years of age, as compared to separately administered DAPTACEL and IPOL.

There is no well-established serological correlate of protection for pertussis. The effectiveness of Quadracel against pertussis was based on a comparison of immune responses (booster response and GMCs) to the pertussis antigens following Quadracel to those following DAPTACEL, which contains the same pertussis antigens manufactured by the same process as those in Quadracel. The efficacy of the pertussis component of DAPTACEL previously was determined in clinical efficacy trials conducted in infants (see DAPTACEL prescribing information for further information).

The effectiveness of Quadracel against the polioviruses, tetanus, and diphtheria was based on a comparison of immune responses following Quadracel to those following DAPTACEL (diphtheria and tetanus) and IPOL (polioviruses). There are scientifically well-established serological correlates of protection for diphtheria, tetanus, and the polioviruses. However, a high proportion of previously vaccinated children 4 through 6 years of age would be expected to have seroprotective levels of antibodies prior to receipt of Quadracel. Thus, for these antigens, the primary evaluation of the effectiveness of Quadracel was based on a comparison of booster response rates and geometric mean antibody concentrations or titers (GMCs or GMTs) relative to separately administered DAPTACEL and IPOL.

The safety of Quadracel was evaluated relative to separately administered DAPTACEL and IPOL.

No major issues were noted with the conduct of either trial, and the results from both trials support licensure.

Study M5I02 (NCT01346293): Primary Study for Immunogenicity and Safety of Quadracel

Study M5I02 was an open-label, randomized, controlled, multi-center US phase 3 trial, designed to examine the safety and immunogenicity of Quadracel as compared to DAPTACEL + IPOL. The study population consisted of children ages $\geq$ 4 and < 7 years who had completed the four dose DTaP series and 3 or 4 dose IPV series with either Pentacel and/or DAPTACEL.

The applicant recruited 3372 subjects into the trial and randomized them to 4 cohorts. Of these 3372 subjects, 3360 subjects received a vaccine (see Table 11). Subjects assigned to a safety and immunogenicity subset were randomized in a 1:1 ratio to Group 1 and Group 2. Groups 3 and 4 were randomized 8:1 for a safety only subset comparing Quadracel to DAPTACEL + IPOL.

Table 11: Study M5I02 Cohorts

Cohort	Population	# Subjects randomized	# Subjects Vaccinated	Purpose
1	Quadracel	324	323	Immunogenicity and Safety
2	DAPTACEL + IPOL	327	327	Immunogenicity and Safety
3	Quadracel	2419	2411	Safety
4	DAPTACEL + IPOL	302	299	Safety

Cohort 1 included 323 vaccinated subjects, of which 303 completed the study to a sufficient degree to be evaluated for immunogenicity. Cohort 2 enrolled and vaccinated 327 subjects, of which 302 were included in the immunogenicity comparison group. Thus a total of 605 subjects were included in the Immunogenicity Full Analysis Set (FAS). Of these subjects, 516 subjects were in included in the Immunogenicity Per-protocol (PP) analysis set.

Subjects in Cohorts 3 and 4 were assigned to the safety-only subset, and did not provide blood samples for immunogenicity evaluations. Eight subjects in cohort 3 did not receive Quadracel vaccination, and three subjects in Group 4 did not receive DAPTACEL + IPOL vaccinations.

Of note, all vaccinated subjects in cohorts 1 and 2 also received concomitant vaccination with MMR vaccine (Measles, Mumps, and Rubella Virus Vaccine Live, Merck and Co, Inc.) and Varicella vaccine (Varicella Virus Vaccine Live, Merck and Co, Inc.) at the time of immunization with the study drug. Most subjects in cohorts 3 and 4 also received concomitant vaccination with MMR and Varicella vaccines, although each of these vaccines were not required for those subjects who could provide documentation of prior receipt of two doses.

Results of Safety Analysis
The primary safety objective of the study was to compare the safety profile of Quadracel alone versus DAPTACEL + IPOL (see section 7 for additional discussion). The applicant demonstrated that Quadracel was safe for its stated indication.

Immunogenicity Statistical Analysis
The co-primary immunogenicity endpoints were post-vaccination booster response rates and antibody GMCs or GMTs for all antigens contained in Quadracel.

The immunogenicity statistical analyses, with criteria for non-inferiority (Quadracel compared to Control vaccines) for each antigen, and definitions of booster response are summarized below.

The primary immunogenicity hypotheses were that the booster response rate for each antigen in the Quadracel arm (cohort 1) would be non-inferior to the booster response-rate in the DAPTACEL + IPOL arm (cohort 2).

- For Pertussis, a booster response was defined using the fold-rise in geometric mean concentration (GMC) of each antibody. In order to correct for the possibility of high pre-vaccination antibody concentrations, the applicant used the following to define a positive booster response.
    - Subjects whose pre-vaccination antibody concentrations were less than the lower limit of quantitation (< LLOQ) for each anti-pertussis (PT, FHA, PRN, and FIM) antibody demonstrated a booster response if they had post-vaccination levels ≥ 4X LLOQ
    - Subjects whose pre vaccination antibody concentrations were ≥ LLOQ but < 4X LLOQ, demonstrated a booster response if they had a 4-fold rise (i.e., post-/pre-vaccination ≥ 4)
    - Subjects whose pre vaccination antibody concentrations were ≥ 4X LLOQ, demonstrated a booster response if they had a 2-fold response (i.e., post /pre vaccination ≥ 2).
- For the tetanus and diphtheria toxoids, antibody GMCs were measured, and a booster response was defined as the following:
    - Subjects whose pre-vaccination antibody concentrations were < 0.1 IU/mL demonstrated a booster response if they had a post-vaccination level ≥ 0.4 IU/mL
    - Subjects whose pre-vaccination antibody concentrations were ≥ 0.1 IU/mL but < 2.0 IU/mL demonstrated a booster response if they had a 4-fold rise (i.e., post-/pre-vaccination ≥ 4)
    - Subjects whose pre-vaccination antibody concentrations were ≥ 2.0 IU/mL, demonstrated a booster response if they had a 2-fold response (i.e., post-/pre-vaccination ≥ 2).
- For IPV, the applicant measured geometric mean neutralization titers (GMT) and defined a booster response as follows:
    - Subjects whose pre-vaccination antibody concentrations were < 1:8 dilution (dil) demonstrated a booster response if they had post-vaccination levels ≥ 1:8 dilution

- Subjects whose pre-vaccination antibody concentrations were ≥ 1:8 dil, demonstrated a booster response if they had a 4-fold rise (i.e., post-/pre-vaccination ≥ 4).

Non-inferiority of Quadracel would be demonstrated if the lower limits of the 2-sided 95% CIs of the difference between groups (Quadracel minus DAPTACEL + IPOL) in post-vaccination booster response rates for each antigen was > -10% and if the lower limit of the 2-sided 95% CIs of the ratio between groups (Quadracel/DAPTACEL + IPOL) in post-vaccination GMCs or GMTs for these antigens was > 0.67.

Based on an analysis of the data submitted by the applicant, non-inferiority was demonstrated for each antigen in Quadracel. The conduct of the statistical analysis and the provided datasets were acceptable. See below for summary immunogenicity data, in tables 12 -17.

Summaries of the per-protocol analysis sets for the booster response rates can be found in tables 12 – 14.

Table 12: Non-Inferiority Comparison of Post-Vaccination Anti-Pertussis Booster Response Rates

Vaccination Group	Quadracel (N[1]=263) N[2]/M[3]	Quadracel (N=263) %	Daptacel + IPOL (N=253) n/M	Daptacel + IPOL (N=253) %	Non-Inferiority Comparison Difference in Rates (%) (Quadracel) – (Daptacel + IPOL)	Non-Inferiority Comparison (95% CI)	Non-Inferiority Achieved (LB of CI > -10)
Anti-PT6	240/252	95.2	222/247	89.9	5.4	(0.7; 10.2)	Yes
Anti-FHA	242/255	94.9	217/248	87.5	7.4	(2.5; 12.5)	Yes
Anti-PRN	246/254	96.9	231/248	93.1	3.7	(-0.2; 7.9)	Yes
Anti-FIM	243/250	97.2	230/249	92.4	4.8	(0.9; 9.1)	Yes

[1] N: total number of subjects
[2] n: number of subjects with booster response
[3] M: number of subjects with available data

Table 13: Non-Inferiority Comparison of Post-Vaccination Anti-Tetanus and Anti-Diphtheria Booster Response Rates Between Groups

Vaccination Group	Quadracel (N[1]=263) N[2]/M[3]	Quadracel (N=263) %	Daptacel + IPOL (N=253) n/M	Daptacel + IPOL (N=253) %	Non-Inferiority Comparison Difference in Rates (%) (Quadracel) – (Daptacel + IPOL)	Non-Inferiority Comparison (95% CI)	Non-Inferiority Achieved (LB of CI > -10)
Anti-tetanus	213/253	84.2	209/248	84.3	-0.1	(-6.5; 6.3)	Yes
Anti-diphtheria	249/256	97.3	247/249	99.2	-1.9	(-4.8; 0.6)	Yes

[1] N: total number of subjects
[2] n: number of subjects with booster response
[3] M: number of subjects with available data

Table 14: Non-Inferiority Comparison of Post-Vaccination Anti-Polio Booster Response Rates Between Groups

Vaccination Group	Quadrace (N[1]=263) N[2]/M[3]	Quadracel (N=263) %	Daptacel + IPOL (N=253) n/M	Daptace + IPOL (N=253) %	Non-Inferiority Comparison Difference in Rates (%) (Quadracel) – (Daptacel + IPOL)	Non-Inferiority Comparison (95% CI)	Non-Inferiority Achieved (LB of CI > -10)
Anti-polio 1	214/249	85.9	204/248	82.3	3.7	(-2.8; 10.1)	Yes
Anti-polio 2	195/249	78.3	196/248	79.0	-0.7	(-7.9; 6.5)	Yes
Anti-polio 3	210/247	85.0	210/248	84.7	0.3	(-6.0; 6.7)	Yes

[1] N: total number of subjects
[2] n: number of subjects with booster response
[3] M: number of subjects with available data

Summaries of the per-protocol analysis sets for the GMC ratios can be found in tables 15-17.

Table 15: Non-Inferiority Comparison of Post-Vaccination Anti-Pertussis GMCs Between Groups

Vaccination Group	Quadracel (N[1]=263) M[2]	Quadracel (N=263) Geometric Mean	Daptacel + IPOL (N=253) M	Daptacel + IPOL (N=253) Geometric Mean	Non-Inferiority Comparison GMC Ratio (Quadracel) / (Daptacel + IPOL)	Non-Inferiority Comparison (95% CI)	Non-Inferiority Achieved (LB of CI > .67)
Anti-PT	261	120.7	252	61.3	1.97	(1.68; 2.31)	Yes
Anti-FHA	263	123.5	253	79.0	1.56	(1.30; 1.88)	Yes
Anti-PRN	262	282.6	252	187.5	1.51	(1.27; 1.79)	Yes
Anti-FIM	260	505.8	253	378.9	1.33	(1.12; 1.60)	Yes

[1] N: total number of subjects

[2] M: number of subjects with available data

Table 16: Non-Inferiority Comparison of Post-Vaccination Anti-Tetanus and Anti-Diphtheria GMCs Between Groups

Vaccination Group	Quadracel (N[1]=263) M[2]	Quadracel (N=263) Geometric Mean	Daptacel + IPOL (N=253)M	Daptacel + IPOL (N=253) Geometric Mean	Non-Inferiority Comparison GMC Ratio (Quadracel) / (Daptacel + IPOL)	Non-Inferiority Comparison (95% CI)	Non-Inferiority Achieved (LB of CI > .67)
Anti-tetanus	262	6.4	253	5.5	1.17	(0.998; 1.38)	Yes
Anti-diphtheria	262	18.6	253	15.5	1.2	(1.01; 1.42)	Yes

[1] N: total number of subjects

[2] M: number of subjects with available data

Table 17: Non-Inferiority Comparison of Post-Vaccination Anti-Polio GMTs Between Groups

Vaccination Group	Quadrace (N[1]=263) M[2]	Quadracel (N=263) Geometric Mean	Daptacel + IPOL (N=253)M	Daptacel + IPOL (N=253) Geometric Mean	Non-Inferiority Comparison GMT Ratio (Quadracel) / (Daptacel + IPOL)	Non-Inferiority Comparison (95% CI)	Non-Inferiority Achieved (LB of CI > .67)
Anti-polio 1	258	3476.9	253	2730.7	1.27	(1.06; 1.52)	Yes
Anti-polio 2	258	3490.9	253	3893.6	0.90	(0.750; 1.07)	Yes
Anti-polio 3	258	4591.4	252	3419.0	1.34	(1.10; 1.64)	Yes

[1] N: total number of subjects

[2] M: number of subjects with available data

Study Td508: Supportive Safety Study
Study Td508 was a randomized, modified double-blinded clinical non-IND Phase 2 study conducted in Canada, to compare the immune responses of Adacel® (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed-TdaP) with those observed following vaccination with Quadracel when given as a fifth dose of a diphtheria-tetanus-acellular pertussis vaccine. This study was conducted to support licensure of Adacel vaccine in Canada. For this study Quadracel was the Canadian licensed comparator vaccine. Of note, Adacel is approved for use in the U.S. as a single booster dose in persons 10 through 64 years of age. Adacel is not approved for use in the U.S. in children younger than 10 years of age.

A total of 294 subjects received Quadracel in Study Td508. CBER review of this trial was limited to the safety data from the Quadracel arm. No study-related serious adverse events (SAEs) were observed and no safety issues were identified.

Conclusions
Based on the clinical data submitted, Quadracel is safe and effective for its intended use.

Results of Bioresearch Monitoring:
Inspections were conducted at four clinical sites under three separate investigators. Three sites were classified as No Action Indicated.
The fourth site was issued a Form FDA 483 with Voluntary Action Indicated. This site had two notable protocol deviations:

1) Product that was subjected to temperature excursions was administered to subjects. However, the excursion was not recognized until after administration.

2) 138 of 347 subjects at this site were ineligible, because they had not completed their primary infant series and boosters with DAPTACEL and/or Pentacel, as required.

These deviations were previously disclosed to the IRB and the sponsor.

These protocol violations were considered in the review of the clinical data. These subjects were removed from the immunogenicity per-protocol analysis group, but were included in the full analysis set. Despite these violations non-inferiority for Quadracel was met for all antigens with similar results in both PP and FAS analyses.

b) Pediatric Research Equity Act (PREA)

The applicant submitted a request for a waiver from the requirement of PREA to conduct studies in pediatric age groups 0 through 6 weeks, 6 weeks to less than 4 years of age, and ages 7 through 16 years. The applicant requested this waiver because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in these age group and is not likely to be used by a substantial number of pediatric patients in these age groups. The waiver request was presented to FDA's Pediatric Review Committee. The Committee and CBER concurred with the waiver request.

c) Clinical Serological Assays

Several clinical assays were used to measure the primary immunogenicity endpoints in pivotal study M5I02. These included the diphtheria (b) (4) assay, a tetanus toxin IgG enzyme linked immunosorbant assay (ELISA), pertussis antigen IgG ELISAs, and a poliovirus (b) (4) assay. Validation reports were provided for all assays. CBER considers the assays adequate for their stated use (i.e. measurement of serum antibody levels). A brief discussion of these assays is below:

i) **Diphtheria**(b) (4) **assay**: This assay directly measures the levels of neutralizing anti-diphtheria toxin antibodies. The validation data for this assay were considered adequate.

ii) **Tetanus toxin IgG ELISA**: This assay measures concentration of anti-tetanus toxin antibodies via an ELISA. The validation data for this assay were considered adequate.

iii) **Pertussis antigens IgG ELISAs:** The pertussis ELISAs measure specific quantities of anti-PT, anti-FHA, anti-FIM 2/3, and anti-PRN IgG. The validation data for each assay were considered adequate.

iv) **Poliovirus** (b) (4) **:** The poliovirus test is an (b) (4) assay that measures the neutralizing antibody response to poliovirus types 1, 2, and 3 in Vero cells. The validation data for this assay were considered adequate.

Conclusions: These serological assays were developed and validated several years ago. The sponsor continues to monitor and provide data to support the continued performance of the assays. Based on the validation data, the assay stability data and the clinical use, for each assay CBER concludes that assay performance is adequate for the stated purpose.

6. Safety

Study M5I02 Safety Analysis:

Overall, adverse events were comparable between the Quadracel and DAPTACEL + IPOL groups in study M5I02 and consistent with adverse events seen in previous studies administering DTaP vaccines.

The data from the M5I02 study showed that the rates of solicited injection site reactions within 7 days and other unsolicited AEs out to 180 days were similar between the Quadracel and the DAPTACEL + IPOL arms of the trial. It was noted that the frequency of Grade 3 injection site erythema was higher in the Quadracel recipients [18.0% (16.6, 19.5)]

within 7 days of vaccination compared to subjects who received Dapatacel + IPOL [11.9% (9.5, 14.8)].These injection site reactions resolved within three days without sequelae and no similar trends were seen for other injection site reactions, including grade 1 or grade 2 erythema, or others that might be expected to co-segregate (e.g., swelling, pain change in limb circumference or extensive limb swelling). No other substantive concerns were raised during the review of the submitted safety data.

See Table 18 below for a summary of solicited adverse events

Table 18: Solicited Adverse Events (Study M5I02

Subjects experiencing at least one:	**Quadracel (N=2733)**		**Either DAPTACEL or IPOL (N=621)**	
Injection site reactions by maximum intensity	**n/M**	**% (95% CI)**	**n/M**	**% (95% CI)**
Injection site pain: Total	2081/2689	77.4 (75.8,79.0)	461/603	76.5 (72.9, 79.8)
Grade 1 (easily tolerated)	1517/2689	56.4 (54.5,58.3)	331/603	54.9 (50.8, 58.9)
Grade 2 (interferes with normal behavior or activities)	511/2689	19.0 (17.5,20.5)	112/603	18.6 (15.5, 21.9)
Grade 3 (incapacitating, can't perform usual activities)	53/2689	2.0 (1.5, 2.6)	18/603	3.0 (1.8, 4.7)
Injection site erythema: Total	1587/2687	59.1 (57.2,60.9)	322/603	53.4 (49.3, 57.4)
Grade 1 (0 <25mm)	849/2687	31.6 (29.8,33.4)	192/603	31.8 (28.1, 35.7)
Grade 2 (≥ 25mm-50mm)	254/2687	9.5 (8.4, 10.6)	58/603	9.6 (7.4, 12.3)
Grade 3 (≥ 50mm)	484/2687	18.0 (16.6,19.5)	72/603	11.9 (9.5, 14.8)
Injection site swelling: Total	1076/2678	40.2 (38.3,42.1)	219/602	36.4 (32.5, 40.4)
Grade 1 (0 <25mm)	630/2678	23.5 (21.9,25.2)	139/602	23.1 (19.8, 26.7)
Grade 2 (≥ 25mm-50mm)	217/2678	8.1 (7.1, 9.2)	37/602	6.1 (4.4, 8.4)
Grade 3 (≥ 50mm)	229/2678	8.6 (7.5, 9.7)	43/602	7.1 (5.2, 9.5)
Change in limb circumference: Total	1703/2500	68.1 (66.3,69.9)	302/464	65.1 (60.6, 69.4)
Grade 1 (increased 0 <25mm from baseline)	1494/2500	59.8 (57.8,61.7)	272/464	58.6 (54.0, 63.1)
Grade 2 (increased ≥ 25mm-50mm from baseline)	205/2500	8.2 (7.2, 9.3)	30/464	6.5 (4.4, 9.1)
Grade 3 (increased ≥ 50mm from baseline)	4/2500	0.2 (0.0, 0.4)	0/464	0.0 (0.0, 0.8)
Extensive Limb Swelling of vaccinated limb: Total*	39/2666	1.5 (1.0, 2.0)	8/598	1.3 (0.6, 2.6)
Systemic reactions				
Temperature ≥ 38.0 °C: Total	161/2668	6.0 (5.2, 7.0)	41/598	6.9 (5.0, 9.2)
Grade 1 (≥ 38.0 °C to ≤ 38.4 °C)	70/2668	2.6 (2.1, 3.3)	18/598	3.0 (1.8, 4.7)
Grade 2 (≥ 38.5 °C to ≤ 38.9 °C)	56/2668	2.1 (1.6, 2.7)	11/598	1.8 (0.9, 3.3)
Grade 3 (≥ 39.0 °C)	35/2668	1.3 (0.9, 1.8)	12/598	2.0 (1.0, 3.5)
Headache: Total	419/2688	15.6 (14.2,17.0)	100/603	16.6 (13.7, 19.8)
Grade 1 (no interference with activity)	320/2688	11.9 (10.7,13.2)	72/603	11.9 (9.5, 14.8)
Grade 2 (some interference with activity)	84/2688	3.1 (2.5, 3.9)	24/603	4.0 (2.6, 5.9)
Grade 3 (prevents daily activity)	15/2688	0.6 (0.3, 0.9)	4/603	0.7 (0.2, 1.7)
Malaise: Total	940/2687	35.0 (33.2,36.8)	200/603	33.2 (29.4, 37.1)

Grade 1 (no interference with activity)	583/2687	21.7 (20.2,23.3)	113/603	18.7 (15.7, 22.1)
Grade 2 (some interference with activity)	286/2687	10.6 (9.5, 11.9)	67/603	11.1 (8.7, 13.9)
Grade 3 (prevents daily activity)	71/2687	2.6 (2.1, 3.3)	20/603	3.3 (2.0, 5.1)
Myalgia: Total	1445/2688	53.8 (51.9,55.7)	317/603	52.6 (48.5, 56.6)
Grade 1 (no interference with activity)	968/2688	36.0 (34.2,37.9)	202/603	33.5 (29.7, 37.4)
Grade 2 (some interference with activity)	425/2688	15.8 (14.5,17.2)	98/603	16.3 (13.4, 19.4)
Grade 3 (prevents daily activity)	52/2688	1.9 (1.4, 2.5)	17/603	2.8 (1.7, 4.5)

n: number of subjects experiencing the endpoint listed in the first two columns

M: number of subjects with available data for the relevant endpoint

*Extensive limb swelling defined as swelling of the injected limb, including the adjacent joint (elbow or shoulder) as compared to baseline.

Unsolicited Adverse Events were also comparable, with 34.8% of subjects in the Quadracel group experiencing at least one unsolicited adverse event and 30.8% in the DAPTACEL + IPOL group experiencing at least one adverse event within 28 days of vaccination.

Within 28 days following vaccination, 0.1% of subjects (3/2733) in the Quadracel group experienced a SAE. During the same time period, 0.2% subjects (1/621) in the DAPTACEL + IPOL group experienced a SAE. Within the 6-month follow-up period after vaccination, SAEs were reported in 0.8% of subjects (21/2733) who received Quadracel and 0.5% of subjects (3/621) who received DAPTACEL + IPOL vaccines. No SAEs were determined to be related to vaccination.

One Adverse Event of Special Interest (AESI) was reported: a recipient of Quadracel was diagnosed with type I diabetes mellitus. However the subject had a family history of type I diabetes and the event was determined to be unrelated to vaccination.

No significant differences in safety outcomes were observed between ethnic subgroups (Caucasian, Black and Hispanic), or sex. The study was not powered to evaluate these differences and the comparisons were descriptive in nature.

The safety data from study M5I02 are supportive of licensure of Quadracel for the proposed indication.

Study Td508:

Safety data from this trial consisted of AE data gathered from the Quadracel arm. These data are summarized in Table 1.

Table 19: Summary Safety Data, Study Td508

Subjects experiencing at least one (by maximum intensity):	**Quadracel (N=294) n/M(%)**
Immediate reactions (within 30 minutes)	7/292 (2.4)
Injection site reactions	
Injection site pain : Total*	195/290 (67.24)
Grade 1	149/290 (51.38)
Grade 2	43/290 (14.83)
Grade 3	3/290 (1.03)
Injection site erythema: Total	150/290 (51.72)
Grade 1 (< 10mm)	40/290 (13.79)
Grade 2 (≥10 to < 35mm)	26/290 (8.97)
Grade 3 (≥ 35mm)	84/290 (28.97)
Injection site swelling: Total	98/290 (33.79)
Grade 1 (< 10mm)	23/290 (7.93)
Grade 2 (≥10 to < 35mm)	25 (8.62)
Grade 3 (≥ 35mm)	50 (17.24)
Change in limb circumference: Total [mean increase from baseline]	124/282 (43/97) [0.61cm]
Increased 0-0.99cm	104/282 (36.88)
Increased 1-1.99cm	16/282 (5.67)
Increased 2-2.99cm	3 (1.03)
Increased ≥ 3cm	1 (0.35)
Rash	41/249 (14.14)
Systemic reactions	
Temperature ≥ 38.0 °C: Total	49/290 (16.90)
Grade 1 (≥ 38.0 °C to ≤ 38.7 °C)	29/290 (10.00)
Grade 2 (≥ 38.8 °C to ≤ 39.4 °C)	15/290 (5.17)
Grade 3 (≥ 39.5 °C)	4/290 (1.38)
Headache (Total)*	49/290 (16.9)
Grade 1	43/290 (14.83)
Grade 2	4/290 (1.38)
Grade 3	2/290 (0.69)
Tiredness or decreased energy (Total)*	106/290 (36.55)
Grade 1	75/290 (25.86)
Grade 2	22/290 (7.59)
Grade 3	9/290 (3.10)
Anorexia (Total)*	64/290 (22.07)
Grade 1	46/290 (15.86)
Grade 2	12/290 (4.14)
Grade 3	6/290 (2.07)

n: number of subjects experiencing the endpoint listed in the first two columns
M: number of subjects with available data for the relevant endpoint

No study-related SAEs were observed and no safety issues were identified.

Conclusions
The safety data from studies M5I02 and Td508 are adequate to support licensure of Quadracel.

Pharmacovigilance:
Quadracel is currently approved for use in several other countries, and based upon a review of the available postmarketing safety data, the applicant has proposed routine pharmacovigilance as well as ongoing monitoring and periodic reporting for the following identified risks: anaphylactic reactions; cellulitis; convulsion including febrile convulsion; Henoch-Schonlein purpura; and hypotonic-hyporesponsive episode (HHE); and of the following potential risks: Brachial neuritis/ radiculitis brachial and Guillain-Barré syndrome (GBS). CBER finds the proposed pharmacovigilance plan acceptable.

7. Advisory Committee Meeting

No issues requiring the input of an Advisory Committee were identified.

8. Other Relevant Regulatory Issues

Not Applicable

9. Labeling

The proprietary name (Quadracel) was reviewed by the Advertising and Promotional Labeling Branch and was found acceptable.

The final version of the package insert is considered acceptable.

The carton and vial labeling were reviewed and found acceptable.

10. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The committee recommends approval of the application.

b) Risk/ Benefit Assessment

No major concerns regarding the safety of this product in its intended population for its intended purpose were raised in the review. The immune responses observed in trial M5I02 were robust and support the effectiveness of this product. Overall, the benefit of this vaccine in preventing the diseases for which it is intended outweighs the minimal risks.

c) Recommendation for Postmarketing Risk Management Activities

The applicant should monitor safety via routine pharmacovigilance.

d) Recommendation for Postmarketing Activities

Sanofi-Pasteur will conduct routine pharmacovigilance.