Pharmacovigilance Plan Review

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Through:	Christopher Jankosky, M.D., M.P.H. Chief PVB/DE/OBE David Martin, M.D., M.P.H. Director, DE/OBE
Subject:	BLA 125525.0
Applicant:	Sanofi Pasteur
Product:	Quadracel Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliovirus (DTaP-IPV) Vaccine
Proposed Indication:	For active immunization against diphtheria, tetanus, pertussis and poliomyelitis in children 4 to 6 years of age (as a 5^{th} dose booster)
Submission Date:	24-MAR-2014
PVP Submission Date:	24-MAR-2014
Assigned to this Reviewer:	08-APR-2014
Action Due Date:	24-MAR-2015

1. **Introduction**

a. Product description

The drug substances used to formulate Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliomyelitis Vaccine (DTaP-IPV) are the same as drug substances used in US licensed Pentacel® vaccine. In addition, the drug product is formulated and filled in US licensed facilities.

b. Pertinent regulatory history

DTaP-IPV was first registered on 20 March, 1997, in Canada and is also currently licensed in Australia, Bermuda and Mexico. This vaccines is indicated for prophylaxis of diphtheria caused by *Corynebacterium diphtheriae*, tetanus caused by *Clostridium tetani*, pertussis (whooping cough) caused by *Bordetella pertussis*, and poliomyelitis caused by polioviruses types 1, 2, and 3. DTaP-IPV vaccine is indicated for primary and booster immunization in children from (b) (4) through 6 years of age (prior to their 7th birthday).

c. PBRER (20-MAR-2012 to 19-MAR-2013)

Approximately (b) (4) doses of Quadracel have been distributed since initial authorization, with approximately (b) (4) doses distributed during the current PBRER reporting period. Age stratified distribution data are not available and therefore the number of doses administered as a booster in children aged from 4 to 6 years of age is unknown.

No Regulatory Authority or MAH actions were taken for safety reasons during the reporting period, based upon routine surveillance including focused review of important identified and potential risks.

d. Pediatric Research Equity Act

The sponsor states “the safety and immunogenicity of Quadracel will only be assessed in individuals who are ≥ 4 years to < 7 years of age: therefore, there is no plan to request deferral of pediatric studies.”

e. Objectives/Scope of the review

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies should the product be licensed.

2. Materials reviewed

Materials reviewed in support of this assessment include the following:

a. Section 1.16.1: Pharmacovigilance Plan (See Section 3)

b. Section 2.7.4: Summary of Clinical Safety

c. Section 5.3.5.1: Reports of Efficacy and Safety Studies:

i. M5I02 Study Report

Pivotal Study M5I02, Safety and Immunogenicity of DTaP-IPV (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliovirus Vaccine) Compared to DAPTACEL® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) + IPOL® (Poliovirus Vaccine Inactivated) as the 5th Dose in Children 4 to 6 Years of Age. (US)

ii. Td508 Study Report

Supportive Study Td508, Safety and Immunogenicity of ADACEL® (TdcP Vaccine) Compared with QUADRACEL® (HCPDT-mIPV Vaccine) as Fifth Dose in Children 4-6 Years of Age. (Canada; TdcP in Canada is the same as TdaP)

d. Section 5.3.6 Reports of Postmarketing Experience

e. PBRER (Reporting period 20-MAR-2012 to 19-MAR-2013)

3. **Pharmacovigilance Plan Review**

a. Clinical safety database

To date, approximately 4185 subjects have been exposed to DTaP-IPV vaccine in Sanofi Pasteur-sponsored clinical studies, completed and ongoing.

The following reactions were identified in the pre-licensure clinical studies, or common reactions associated with vaccination in the pediatric population:

Crying	Limb swelling
Fever	Rash
Injection site reactions	Vomiting
Irritability	

b. Postmarketing Experience

From 20-MAR-1997 through 20-SEP-2013, a total of 348 spontaneous case reports have been received, including 65 (18.7%) classified as serious; 156 (44.8%) of the total reports involved children ages 4 through 6 years, of which 22 (14.1%) were classified as serious.

c. Postmarketing safety signals

Vasovagal reactions

A single, unconfirmed safety signal, vasovagal reaction, was closed by the sponsor during the most recent reporting period, 20-MAR-2012 to 19-MAR-2013, after evaluation of all reports of possible vasovagal reaction (presyncope, syncope, loss of consciousness).

Two reports were identified and were confounded by co-administration of one or more other vaccines. Review of the literature indicates that vasovagal reactions associated with vaccination occur typically in adolescents 11-18 years of age, particularly females, although a group of 5 reports of children less than 7 years of age who received DTaP-IPV-containing vaccines in New South Wales, Australia in 2011 mention syncope.

d. Safety concerns (labeled)

i. Important identified safety issues
   1. Anaphylactic reaction
   2. Convulsions (including febrile convulsion)
   3. Hypotonic-hyporesponsive episode (HHE)

ii. Important potential safety issues
   1. Guillain-Barré syndrome (GBS)
   2. Brachial neuritis

   These two issues were identified by a 2011 US Institute of Medicine review of tetanus toxoid-containing vaccines. To date, no cases of GBS or brachial neuritis have been reported following administration of a Sanofi Pasteur DTaP-IPV vaccine.

e. Periodic Benefit Risk Evaluation Report (PBRER)

The following identified and important potential risks are periodically reviewed and reported in the PBRER:

Identified Risks:
1. Anaphylactic reactions
2. Cellulitis
3. Convulsion including febrile convulsion
4. Henoch-Schonlein Purpura
5. Hypotonic-Hyporesponsive Episode (HHE)

Important Potential Risks:
1. Brachial neuritis/ Radiculitis brachial
2. Guillain-Barré syndrome (GBS)

f. Important missing information

Quadracel has not been studied in:
1. Infants less than 2 months of age
2. Children after the sixth year of life
3. Premature infants
4. Pregnant and lactating woman
5. Immunocompromised individuals (secondary to underlying pathologies or iatrogenic immunosuppression)
6. Individuals with bleeding disorders contraindicating IM administration

7. Individuals with severe chronic illness, including cardiac and renal impairments.

g. Sponsor's proposed actions and timelines

Enhanced pharmacovigilance activities proposed by sponsor: in addition to routine pharmacovigilance all identified and potential risks are specifically monitored and addressed in the PSURs/PBRERs.

4. Review of other information from the Managed Review process

Pertinent positive information suggesting a safety signal from the clinical or statistical reviewer: None to date

5. Sections of the licensing application selected by the OBE/DE reviewer

a. Pivotal Study M5I02

Title:
Safety and Immunogenicity of DTaP-IPV (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Inactivated Poliovirus Vaccine) Compared to DAPTACEL® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) + IPOL® (Poliovirus Vaccine Inactivated) as the 5th Dose in Children 4 to 6 Years of Age. (US)

Study population:
Overall, the ratio of males to females was balanced in Study M5I02 (51.5% [1728/3354] males to 48.5% [1626/3354] females); 51.5% (1408/2733) and 51.5% (320/621) of subjects were male, in the DTaP-IPV and DAPTACEL + IPOL groups, respectively. The mean age was 4.4 years for both treatment groups and the majority of the subjects were Caucasian (75.7% [2538/3354]), Black (8.6% [290/3354]), or Hispanic (7.9% [265/3354]). The QUADRACEL group had a nominally higher proportion of Caucasian subjects (76.7%), a lower proportion of Black subjects ((8.3%) and a lower proportion of subjects designated as Other Race (5.6%) as compared to the DAPTACEL + IPOL group, with Caucasian subjects (71.3%), Black subjects (10.3%) and Other Race subjects (9.2%).

Subject disposition:
Of the randomized subjects, a total of 2734 subjects ages 4 to 6 years received 1 dose of DTaP-IPV and 626 subjects received 1 dose of both DAPTACEL and IPOL in study M5102; 2745 (96.5%) and 599 (95.2%) subjects in the DTaP-IPV and DAPTACEL + IPOL groups, respectively, completed the study through the 180 day follow-up.

Discontinuations included: 67 (2.4%) and 21 (3.3%) overall; 30 (1.1%) and 9 (1.4%) for non-compliance with protocol; 21 (0.7%) and 8 (1.3%) who were lost to follow-up; and 15 (0.5%) and 4 (0.6%) who withdrew voluntarily, not for an

adverse event, in the DTaP-IPV and DAPTACEL + IPOL groups, respectively. No discontinuations due to adverse events (serious or non-serious) were reported in either group.

Safety Results
All safety analyses were performed on the Safety Analysis Subset (SafAS), which included all subjects who received the study or control vaccine, analyzed by the actual vaccine received, regardless of randomization. Only subjects who did not receive a vaccine corresponding to one of the study groups were excluded from the SafAS.

Deaths
No deaths were reported through study Day 180.

Serious Adverse Events (SAEs)
A total of 21/2733 (0.8%) subjects in the QUADRACEL group and 3/621 (0.5%) subjects in the DAPTACEL + IPOL group experienced SAEs during the study. Hospitalization was reported for 18/2733 (0.7%) subjects in the QUADRACEL group and 3/621 (0.5%) subjects in the DAPTACEL + IPOL group.

Within the initial 28 days of the study, the proportion of subjects experiencing at least one SAEs occurring was 3/2733 (0.1%) and 1/621 (0.2%) in the QUADRACEL and DAPTACEL + IPOL groups, respectively.

SAEs by System Organ Class (SOC)
The number (percentage) of patients experiencing an SAE by SOC included Gastrointestinal disorders: 3 (0.1%) and 3 (0.5%); Immune system disorders: 1 (<0.1%) and 0; Infections and infestations 7 (0.3%) and 1 (0.2%); Injury, poisoning and procedural complications: 0 and 1 (0.2%); Metabolism and nutrition disorders: 2 (0.1%) and 0; Musculoskeletal and connective tissue disorders: 0 and 1 (0.2%); Nervous system disorders: 2 (0.1%) and 0; Respiratory, thoracic and mediastinal disorders: 6 (0.2%) and 0, in the QUADRACEL and DAPTACLE + IPOL groups, respectively.

Solicited Local Reactions
The rates of specific solicited local reactions (injection site pain, injection site erythema, injection site swelling and change in limb circumference) occurring within 14 days following vaccination were similar in the QUADRACEL group as compared to the DAPTACEL + IPOL group (Section 2.7.4, Table 2.3), noting that the latter group received separate two injections. Extensive limb swelling, a local reaction of particular interest defined as swelling of injected limb including an adjacent joint – elbow and/or shoulder, occurred in 1.5% of QUADRACEL subjects and 1.3% of DAPTACEL + IPOL subjects(Section 2.7.4, Table 2.5).

Solicited Systemic Reactions

The rates of specific solicited systemic reactions (fever, headache, malaise and myalgia) occurring within 7 days of vaccination were similar in the QUADRACEL group as compared to the DAPTACEL + IPOL group (Section 2.7.4, Table 2.11).

Unsolicited Adverse Events
The rate of unsolicited adverse events occurring within 28 days after vaccination was slightly higher in the QUADRACEL group (34.8%) as compared to the rate in the DAPTACEL + IPOL group (30.8%). The rate of non-serious AEs was also slightly higher in the QUADRACEL group (34.8%) vs. the DAPTACEL + IPOL group (30.6%). The rates of immediate unsolicited AEs (0.9% vs. 1.0%) and serious AEs (0.1% vs. 0.2%) in the QUADRACEL and DAPTACEL + IPOL groups, respectively (Section 2.7.4, Table 2.14).

Adverse Events of Special Interest (AESIs)
The following events occurring from Day 0 through Day 28 were pre-defined as AESIs and reported as SAEs:

a. Anaphylactic reactions
b. Autoimmune disorders
c. Hypotonia
d. Hypotonic-hyporesponsive episode (HHE)
e. Seizures (febrile and non-febrile), other neurological events

Only one AESI was reported through Day 28. An individual in the QUADRACEL group developed an autoimmune disorder, namely, Type 1 diabetes, with onset of symptoms 11 days after vaccination.

Concomitant Vaccinations
Upon CBER request, an observational objective was included to describe the safety profile of subjects who did and did not receive MMR and varicella vaccines concomitantly with DTaP-IPV or DAPTACEL + IPOL. However the proportion of subjects who did not receive concomitant vaccination represented a small fraction of the overall SafAS, although they were equally distributed between the QUADRACEL and DAPTACEL + IPV groups, and therefore a true comparison could not be performed. The trends of solicited and unsolicited reactogenicity appeared to be similar to that in MMR + V recipients.

Reactogenicity after 4^{th} vs. 5^{th} Dose of IPV
Another observational safety objective examined the safety profiles of subjects receiving IPV either as 4th or 5th dose and reported no apparent increase in reactogenicity with the 5th dose of IPV.

Supportive Study Td508[1, 2]

Title: Safety and Immunogenicity of ADACEL® (TdcP Vaccine) Compared with QUADRACEL® (HCPDT-mIPV Vaccine) as Fifth Dose in Children 4-6 Years of Age.

1. The study was conducted in Canada where Tdap is referred to as TdcP.
2. The final study report was completed in December 2004.

Study population:
Overall, the ratio of males to females was balanced in Study Td508 (48.81% [288/590] males to 51.19% [302/590] females) overall, with 48.32% (144/298) and 49.32% (144/292) male subjects in the ADACEL and QUADRACEL groups, respectively. The mean age was 4.6 years for both treatment groups and the majority of subjects in both vaccine groups were Caucasian, with 92.95% (277/298) and 90.75% (265/292) in the ADACEL and QUADRACEL groups, respectively.

Subject disposition:
Following randomization, 1 subject from the ADACEL group and 2 from the QUADRACEL group withdrew prior to receiving study vaccine and were not included in either the Intent-to-Treat (ITT) or per-protocol (PP) populations.

A total of 298 children received 1 dose of ADACEL and 297 (99.33% of those randomized) completed the study while a total of 292 children received 1 dose of QUADRACEL and 291 (99.98% of those randomized) completed the study.

Discontinuations
No discontinuations were the result of adverse events (serious or non-serious) in either group. Discontinuations after vaccination included: 2 (0.67%) and 3 (1.02%) overall; 0 and 1 (0.34%) were withdrawn for protocol non-compliance; and 2 (0.67%) and 2 (0.68%) voluntarily withdrew in the ADACEL and QUADRACEL groups, respectively.

Serious Adverse Events
No deaths were reported; 1 SAE was reported in an ADACEL recipient with pre-existing phimosis scheduled for elective circumcision during the study.

Solicited Adverse Events
Primary Safety Endpoints (Days 0-14)
The proportion of subjects reporting any of the four solicited primary safety endpoints was lower in the ADACEL group as compared to the QUADRACEL group. Erythema (34.56% vs. 51.72%), Swelling (24.16% vs. 33.79%), Pain (39.60% vs. 67.24%) and Fever ≥38.0º C (8.72% vs. 16.90%) were reported during Study Days 0-14, in the ADACEL and QUADRACEL groups, respectively. A similar relationship was seen for these same primary safety endpoints during Study Days 0-3. The upper limit of the two-sided 90% CI for the difference between the rate in the ADACEL group and the rate in the QUADRACEL group

was < 10% for each of these safety endpoints, meeting the study's pre-specified criteria for non-inferiority for both 0-3 Days and 0-14 Days periods, given the study's sample size.

Other Solicited Local Adverse Events (Days 0-14)
The proportion of subjects reporting Underarm lymph node swelling was lower in the ADACEL group as compared to the QUADRACEL group: (5.37% vs. 8.28%),

The proportion of subjects reporting Change in limb circumferences was similar in the ADACEL group as compared to the QUADRACEL group: (1.03% vs. 1.06%).

Solicited Systemic Reactions (Days 0-14)
The proportion of subjects reporting each of the following solicited systemic reactions was lower in the ADACEL group as compared to the QUADRACEL group, although in many cases the differences were quite small. Fever (8.72% vs. 16.90%), Chills (7.05% vs. 10.00%), Generalized Body Ache and/or Muscle Weakness (6.38% vs. 8.28%), Tiredness and/or Decreased Energy (31.54% vs. 36.55%), Nausea (9.40% vs. 10.00%), Vomiting (8.05% vs. 10.00%), Headache (16.44% vs. 16.90%), Sore and/or swollen joints (4.43% vs. 4.48), Anorexia (21.48% vs. 22.07%) and Rash (8.39% vs. 14.14%) were reported during Study Days 0-14, in the ADACEL and QUADRACEL groups, respectively.

The proportion of subjects reporting Diarrhea was higher in the ADACEL group as compared to the QUADRACEL group: (14.43% vs. 9.66%),

Immediate Reactions
All participants were observed at the study site for 30 minutes following vaccination and no Serious Adverse Events (SAEs) or cases of anaphylaxis were observed. A total of 14 participants (7 in the ADACEL group and 7 in the QUADRACEL group) experienced 18 adverse events: redness (7 events), swelling (3 events), bruising (3 events), pain (1 event), injection site blanching (1 event), pruritus (1 event), rash (1 event) and erythema (1 event). All participants were reported to have recovered without sequelae.

Unsolicited Adverse Events
A higher proportion of subjects in the ADACEL group reported unsolicited adverse events, 127 (42.62%) vs. 115 (39.38%), for the ADACEL group. For unsolicited adverse events occurring at a frequency of ≥ 1.0%, the Adacel group had higher rates of Ear pain, Abdominal pain (NOS), Injection site bruising, Nasopharyngitis, Ear infection (NOS), Nasal congestion, Rhinorrhoea, Asthma (NOS), and Pharyngitis, while the Quadracel group had higher rates of Injection site erythema, Otitis media (NOS) and Cough.

Additional Adverse Events not Specified in the Protocol
A total of 4 additional AEs not specified in the protocol were collected: Whole Arm Swelling, New Onset Diabetes, Seizure and New Onset Autoimmune Disease. There were no cases of these AEs reported in either group during the course of the study.

Adverse Events of Special Interest
No AESIs were predefined for collection in this study.

6. Integrated Risk Assessment
No safety issue has been identified from review of the submitted study data or from other sources that would trigger a PMR or REMS, require further CBER assessment or any mitigation strategy.

7. **Recommendations:**
   a. Routine pharmacovigilance
   b. Continued monitoring with periodic reporting for the following events, as proposed by the sponsor:

      Identified Risks:
      1. Anaphylactic reactions
      2. Cellulitis
      3. Convulsion including febrile convulsion
      4. Henoch-Schonlein Purpura
      5. Hypotonic-Hyporesponsive Episode (HHE)

      Important Potential Risks:
      1. Brachial neuritis/ Radiculitis brachial
      2. Guillain-Barré syndrome (GBS)