

Pharmacovigilance Plan Review

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Subject: STN 125563.0

Applicant: MCM Vaccines Company
(originally submitted by Sanofi Pasteur)

Product: PR5I
(b) (4) (proposed trade name)
Diphtheria and Tetanus Toxoids and Acellular Pertussis
Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b
Conjugate [Meningococcal Protein Conjugate] and Hepatitis B
[Recombinant] Vaccine (DTaP-IPV-Hib-HepB)

Proposed Indication: Active immunization against diphtheria, tetanus, pertussis,
poliomyelitis, hepatitis B, and invasive disease due to
Haemophilus influenzae type b (Hib) as a three dose series in
children from 6 weeks through 4 years of age

(b) (4) is anticipated to be administered in the US to
healthy infants at 2, 4 and 6 months of age given concomitantly
with currently licensed pediatric vaccines given at the same
age.

CBER Receipt Date: 12-AUG-2014

PVP Submission Date: 12-AUG-2014

Action Due Date: 12-AUG-2015

1. Introduction

a. Product description

PR5I (proposed trade name: (b) (4)) is a hexavalent vaccine being co-developed by Sanofi Pasteur and Merck Sharp & Dohme Corp to provide protection against 6 childhood diseases. PR5I is designed to provide active immunization against diseases caused by *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, poliovirus types 1, 2, and 3, *Haemophilus influenzae* type b, and hepatitis B virus. The vaccine under development is a combination vaccine containing components of vaccines currently licensed in the United States (U.S.), the European Union (EU), and other countries.

Background

Phase 1/2 studies evaluated previous formulations of PR5I and of the PRP-OMPC-containing formulations [PR5I (3, 10), PR5I ((b) (4)) and PR5I ((b) (4)) the formulation with the lowest amount of PRP and HBsAg [PR5I (3, 10)] - containing 3 ug PRP antigen and 10 ug HBsAg - had the lowest rate of fever and systemic adverse experiences. Therefore, PR5I (3,10) was selected for further development based on a slightly more favorable safety and tolerability profile, compared to the other PR5I formulations studied and a subsequent Phase 2 study of that PR5I formulation was conducted in Canada.

Phase 3 protocols 05 and 06 were conducted in the U.S. to evaluate the safety, tolerability and immunogenicity of PR5I in the U.S.-specific immunization schedule to support licensure in the U.S. and those safety data are reviewed in this document.

Phase 3 protocols 07 and 08 were conducted in the EU to assess PR5I using EU-specific immunization schedules to support licensure of PR5I in the EU. Protocols PRI01C and PRI02C evaluated PR5I using country-specific immunization schedules in the United Kingdom and Spain, respectively. Final study reports for these studies are not available but descriptive summaries of important safety outcomes are included.

b. Regulatory

Marketing

No PR5I vaccine (US proposed trade name: (b) (4)) has been marketed as of the date of the submission of the application.

Pediatric Waiver

The sponsor is requesting a partial waiver for children less than 6 weeks of age and 5 years and older, citing Pediatric Research Equity Act (PREA) of 2007 justification:

Infants less than 6 weeks of age:

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 (infants less than 6 weeks of age)

Children 5-17 years of age:

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 (pediatric population 5 years to 17 years of age).

- c. Objectives/Scope of the review (e.g., 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

- a. Section 1.16 Risk Management Plan, including Pharmacovigilance Plan
- b. Pertinent sections of the licensing application selected by the reviewer
 - Section 2.5 Clinical Overview: 5. Overview of Safety
 - Section 2.7.4 Summary of Clinical Safety
 - Section 2.7.6 Clinical Synopses: 2. Adverse Events
 - Section 3.5.3 Integrated Summary of Safety
- c. Postlicensure Safety Data
 - PR5I has not been licensed in any country.

3. Pharmacovigilance Plan Review

a. Clinical Safety Database

The PR5I clinical development program included more than 9400 subjects in 10 clinical studies. Approximately 5600 subjects have received the final formulation of PR5I in Protocols 004, 005, 006, 007, 008, PRI01C and PRI02C.

Phase 1 and 2 Studies (Canada)

Protocols 001, 002 and 003 were Phase 1/2 studies using an earlier formulation of the hexavalent vaccine to evaluate the safety and immunogenicity of a booster dose at 15 to 18 months of age (Protocol 001) and a 4 dose regimen (i.e., an infant series plus a toddler dose) of varying doses of the hexavalent vaccine (Protocols 002 and 003).

Protocol 004 was a Phase 2 study using the final formulation of PR5I and intended to support initiation of the Phase 3 clinical development program. The study enrolled 307 subjects who received PR5I and 153 subjects who received Pentacel and Engerix-B at 2, 4, 6 and 15 months of age. Subjects were followed

for daily temperatures, solicited injection-site and systemic adverse events through Day 7; all adverse events through Day 30; and serious adverse events throughout the study.

Phase 3 Studies

Studies conducted in the U.S. evaluated the safety, tolerability and immunogenicity of PR5I in the U.S.-specific immunization schedule to support licensure in the U.S., while studies conducted in the EU assessed PR5I using EU-specific immunization schedules and will support licensure of PR5I in the EU.

EU Studies

Protocols 007, 008, PRI01C and PRI02C are reported as ongoing in the European Union. The EU studies utilize vaccination schedules that differ from the schedule used in the US studies and incorporate concomitant vaccinations that are relevant to EU countries. These studies are intended to demonstrate that PR5I has a safety profile similar to licensed vaccines containing the same or similar antigens.

Protocol 007 Preliminary Safety Results

Protocol 007, conducted at 40 study centers across Finland, Germany, and Belgium, was designed to evaluate the safety, tolerability and immunogenicity of PR5I when administered at 2, 3, 4, and 12 months of age concomitantly with licensed pediatric vaccines (Prevnar 13™, RotaTeq™, and ProQuad™). This double-blind, randomized, active-comparator controlled Phase III study enrolled 1250 healthy infants (46 to 74 days of age at enrollment). Serious adverse events were reported during Day 1 to Day 15 post vaccination by 17 subjects in the PR5I group and 13 subjects in the INFANRIX™ hexa group and reported as occurring outside the study period for 5 subjects in the PR5I group and 10 subjects in the INFANRIX™ hexa group. No deaths have been reported in this study.

Protocol 008 Preliminary Safety Results

Protocol 008, conducted at 23 study centers across Finland, Italy, and Sweden, was designed to assess the safety, tolerability, and immunogenicity of PR5I when administered at 2, 4, and 11 to 12 months of age concomitantly with licensed pediatric vaccines (Prevnar 13™ and RotaTeq™/ Rotarix™). This double-blind, randomized, active-comparator controlled Phase III study enrolled 1315 healthy infants (46 to 89 days of age at enrollment). Serious adverse events were reported Day 1 to Day 15 post vaccination by 5 subjects in the PR5I group and 7 subjects in the INFANRIX™ hexa group and reported as occurring outside the study period for 1 subject in the PR5I group and 2 subjects in the INFANRIX™ hexa group. No deaths have been reported in this study.

US Studies Submitted to Support US Licensure Combined Data from Protocols 005, 006

PR5I was administered as 2, 4 and 6 months of age and of note, per protocol, PR5I was not administered at the Toddler dose. Safety evaluations for PR5I were conducted during the infant series and between the infant series and toddler dose.

Key Safety Analyses

There were no adverse events of special interest identified *a priori*.

Solicited systemic adverse events (pyrexia, vomiting, crying, somnolence, decreased appetite, irritability) occurring on Days 1 to 5 following any vaccination; solicited injection-site adverse events (redness, swelling, and pain/tenderness/soreness) occurring Days 1 to 5 following any vaccination visit; and unsolicited adverse events Days 1-14 following any vaccination visit but occurring in at least 1% of the subjects in either vaccination group were evaluated using point estimates with 95% confidence intervals provided for vaccination group difference.

Unsolicited adverse events occurring within 15 days following any vaccination and occurring in at least 1% of the subjects in either vaccination group were evaluated using point estimates with 95% confidence intervals provided for vaccination group difference, while less frequent unsolicited adverse events occurring in less than 1% of the subjects in both vaccination group (including serious adverse events collected throughout the study) were summarized descriptively by using point estimates for each vaccination group.

Vaccinations

Protocols 005 (non-inferiority study) and 006 (lot consistency study) included 981 and 2399 subjects, respectively, who received PR5I, while 484 and 401 subjects, respectively, received the two control vaccines, Pentacel and Recombivax HB. These vaccinations were administered at 2, 4 and 6 months of age. NOTE: PR5I was not administered at the Toddler dose.

Concomitant vaccines in Protocol 005 included Prevnar 13 and RotaTaq at 2, 4 and 6 months and at 15 months, toddler doses of DAPTACEL, PedvaxHIB and Prevnar 13 in the PR5I group and DAPTACEL, ActHIB and Prevnar 13 in the Control group.

Concomitant vaccines in Protocol 006 included Prevnar 13 and RotaTaq at 2, 4 and 6 months and at 15 months, toddler doses of PENTACEL and Prevnar 13 in both the PR5I and Control groups.

Study Results

Demographics

The distribution of gender, race, age and weight at enrollment were generally similar between the PR5I and Control group. The two studies randomized 2250 male subjects (52.6%) and 2031 female subjects (47.4%) with a mean age of subjects at enrollment of 64.8 days (range: 46 days to 89 days) and mean subject weight of 5.2 kg (range: 3 kg to 9 kg). Most subjects were classified by race as White (71.7%) of whom 82% were of Non-Hispanic or Latino ethnicity (81.8%), followed by Black (11.0%), Multi-racial (8.6%), Other (6.2%), American Indian or Alaskan Native (4.5%), Asian (3.5%) and Native Hawaiian or Other Pacific Island (0.7%).

Subject Disposition

4281 subjects were randomized (3392 subjects to the PR5I group and 889 subjects to the Control group) including 3380 subjects who were vaccinated with at least one dose of PR5I and 885 were vaccinated with at least one dose of Control vaccine. 3986 subjects (93.1%) completed the infant series (3 doses of PR5I or Control administered at 2, 4, and 6 months of age) and 3593 (83.9%) subjects completed the toddler dose vaccinations (which did not include PR5I and is not a subject of this safety review). There were no notable differences between the 2 vaccination groups regarding discontinuation rates at any stage of the study.

Of the 279 subjects (6.5%) who did not complete the infant series (224 subjects (6.6%) in the PR5I group and 55 subjects (6.2%) in the Control group), the most frequent reasons were Withdrawal by Subject (subject's parent/guardian), Lost to Follow-up, and Protocol Violation. Discontinuation from the study due to an adverse event occurred in 6 subjects (0.2%) in the PR5I group and 1 subject (0.1%) in the Control group.

Of the 392 subjects who discontinued between the infant series and Toddler dose, 311 subjects (9.2%) were in the PR5I group and 81 subjects (9.1%) in the Control group. The most frequent reasons for discontinuations were Lost to Follow-up, Withdrawal by Subject (subject's parent/guardian) and Protocol Violation. Discontinuation from the study due to an adverse event occurred in 2 subjects (0.1%) in the PR5I group and none in the Control group.

Discontinuations due to AEs

Note: Death, itself, was not considered as an adverse event leading to discontinuation unless the subject was discontinued from the study as a result of an adverse event prior to death.

Seven subjects discontinued during the infant series within 15 days following vaccination due to an adverse event: 6 subjects (0.2%) in the PR5I group and 1 subject (0.1%) in the Control group. Two subjects discontinued between the

infant series and Toddler dose due to an adverse event: 2 subjects (0.1%) in the PR5I group and none in the Control group.

Discontinuations during the infant series in the PR5I group included: Injection site erythema, pain and swelling after Dose 2 (resolved); Hydrocephalus after Dose 2 (fatal); Failure to thrive after Dose 1 (resolved); Constipation, Crying, Decreased appetite, Irritability, Injection-site erythema, pain and swelling, irritability and somnolence after Dose 1 (resolved); Gastrointestinal disorder after Dose 3 (outcome unknown); ITP after Dose 2 (resolving); Colitis (resolved with sequelae – not specified in the study report); and Myoclonus after dose 1 (resolved). A single discontinuation occurred during the infant series in the Control group due to Irritability after Dose 1 (resolved).

Adverse Events

One or more adverse events were reported by 3195 subjects (94.8%) in the PR5I group and 818 subjects (93.0%) in the Control group within 15 days following any infant vaccination. Systemic adverse events were reported by 3150 subjects (93.5%) in the PR5I group and 795 subjects (90.3%) in the Control group. Serious adverse events were reported by 42 subjects (1.2%) in the PR5I group and 11 subjects (1.3%) in the Control group (Day 1 to Day 15). Adverse events leading to study vaccine discontinuation were reported by 8 subjects (0.2%) in the PR5I group and 1 (0.1%) in the Control group. A higher percentage of subjects in the PR5I group reported ≥ 1 adverse events within 14 days after vaccination as compared to the control group with a difference estimate of 2.1 (95% CI: 0.2, 4.3). This difference was largely due to an increased rate of pyrexia in the PR5I group (discussed below).

Deaths

Deaths occurred in 6 out of 3370 subjects in the PR5I group (0.2%) and 1 out of 880 subjects in the Control group (0.1%). The following PTs were reported with the outcome of death in the PR5I group: asphyxia (b) (6) days after Dose 2, hydrocephalus (b) (6) after Dose 2, death not otherwise characterized (b) (6) days after Dose 1, sepsis (b) (6) days after Dose 1, and two reports of sudden infant death syndrome - one occurring (b) (6) days after dose 2 and one occurring (b) (6) days after Dose 1. A single death occurred in the control group with the PTs: pneumonia, aspiration, cardiac arrest and respiratory arrest occurring (b) (6) days after Dose 1.

Serious Adverse Events (SAEs)

In US studies, one or more SAE after any infant dose vaccination was reported by 143 subjects (4.2%) in the PR5I group and 45 subjects (5.1%) in the Control group. The studies' sample sizes limit the ability to detect differences in the reported rates of SAEs.

Proportions of subjects reporting SAEs by MedDRA System Organ Class for the PR5I and Control groups, respectively, for the entire study periods included: Blood and lymphatic system disorders (0% and 0.5%), Cardiac disorders (0%

and 0%), Congenital, familiar and genetic disorders (0% and 0.1%), Gastrointestinal disorders (0.4% and 0%), General disorders and administration site conditions (0.3% and 0.1%), Infections and infestations ((2.7% and 3.4%), Injury, poisoning and procedural complications (0.3% and 0.5%), Investigations (0% and 0%), Metabolism and nutrition disorders (0.7% and 0.6%), Nervous system disorders (0.3% and 0.5%), Renal and urinary disorders (0.1% and 0.0%), Respiratory, thoracic and mediastinal disorders (0.5% and 0.8%), Vascular disorders (0% and 0.1%).

Proportions of subjects reporting SAEs by MedDRA Preferred Terms with more than two SAEs in either the PR5I and Control groups, respectively, for the entire study periods included: Gastroesophageal reflux disease (0.2% and 0%), Pyrexia (0.1% and 0.1%), Bronchiolitis (0.4% and 0.9%), Croup infections (0.2% and 0.3%), Gastroenteritis (0.3% and 0%), Gastroenteritis viral (0.1% and (0.0%), Pneumonia (0.2% and 0.2%), Respiratory syncytial virus bronchiolitis (0.5% and 0.9%), Subcutaneous abscess (0.1% and 0.1%), Upper respiratory tract infection (0.1% and 0.1%), Urinary tract infection (0.1% and 0.2%), Viral infection (0.1% and 0%), Skull fracture (0.1% and 0.1%), Dehydration (0.6% and 0.3%), Febrile convulsion (0.1 and 0%), Bronchial hyperreactivity (0.1% and 0.1%), Respiratory distress (0.1% and 0.2%)

Solicited Injection Site Reactions

Solicited injection-site adverse events were reported by 2749 subjects (81.7%) in the PR5I group and 709 subjects (80.6%) in the Control group. Pain was the most common solicited injection site reaction in both vaccination groups (71.2% in PR5I and 72.0% in Control); there was no increase in the frequency with subsequent vaccinations in either group. A statistically significant increase in the proportion of subjects with injection-site erythema was reported in the PR5I group (46.0%) as compared to the Control group (41.3%); the majority of the injection-site erythema reactions were <2.5 cm (mild).

NOTE: The injection-site adverse events for Prevnar 13™ (one of the concomitantly administered licensed pediatric vaccines) were not integrated and are not presented in the Summary of Clinical Safety

Solicited Systemic Reactions

Solicited systemic adverse events (crying, decreased appetite, irritability, somnolence and vomiting) were collected on the Vaccine Report Card (VRC) daily from Day 1 (day of vaccination) through Day 5 following any infant dose vaccination. In addition, the parent/legal guardian recorded daily temperatures (taken with study provided calibrated digital thermometers) for 5 days following each vaccination. For temperatures $\geq 38.0^{\circ}\text{C}$ rectally, subjects were evaluated for confounding by an intercurrent illness; if not considered confounded, the elevated temperature was captured as a solicited systemic adverse event of pyrexia. This resulted in slightly lower rates of pyrexia as compared to elevated temperatures.

One or more solicited systemic adverse events were reported by 3090 subjects (91.7%) in the PR5I group and 782 subjects (88.9%) in the Control group. The incidence of crying, decreased appetite, irritability, somnolence and vomiting was comparable between PR5I and Control (the difference estimate confidence intervals contained 0). However, pyrexia was reported in 47.2% of the subjects in the PR5I group and 33.6% of the subjects in the Control group [difference estimate 13.6 (95% CI: 9.7, 17.3)].

Pyrexia

A statistically significant higher incidence of pyrexia (temperature $\geq 38^{\circ}\text{C}$) was observed after PR5I vaccinations (49.1%), as compared to Control (35.6%), with the estimated difference of 13.3% (95% CI: 9.4, 17.0). Higher rates (22.9%, 2.3%, respectively) of more severe pyrexia ($\geq 38.5^{\circ}\text{C}$, $\geq 39.5^{\circ}\text{C}$) as compared to infants receiving PENTACEL (13.7%, 1.2%, respectively) were also seen. The increase in pyrexia in the PR5I group did not result in an increase in hospitalizations or other fever-related medical events. There were no reports of convulsion (febrile or afebrile) within 15 days after any infant dose vaccination.

The incidence of pyrexia increased from Dose 1 to Dose 2 and then largely stabilized from Dose 2 to Dose 3 and was consistently higher in the PR5I group as compared to the Control group. Similar trends for pyrexia by dose were noted over the infant dose series for PR5I (18.1%, 27.4%, 28.0% for Doses 1, 2, and 3, respectively) and Control (13.9%, 17.1%, 17.1%, for Doses 1, 2, and 3, respectively).

Most of the pyrexia was classified as mild to moderate in severity, of brief duration (≤ 2 days for the vast majority of events), and no occurrence led to hospitalization or resulted in study discontinuation. Pyrexia was classified as serious in 3 cases, all in the PR5I group (0.1%) and included one subject with Group A streptococcus sepsis and 2 subjects for whom no infectious cause for fever was identified.

Unsolicited Systemic Adverse Events

The incidence of unsolicited AEs within 15 days following vaccination was slightly higher in the PR5I group (43.1%) as compared to the Control group (39.5%). The most frequent unsolicited systemic adverse events reported were upper respiratory tract infection (8.5% in the PR5I group and 8.4% in the Control group), diarrhea (5.7% in the PR5I group and 4.1% in the Control group), and otitis media (4.4% in the PR5I group and 6.0% in the Control group). All rate differences between the PR5I and Control groups for specific types of unsolicited systemic AEs with incidence of $\geq 1\%$ in either vaccination group were comparable between the two vaccination groups.

Limitations of the Clinical Safety Data

Protocols 005 and 006 evaluated safety data from a total of 3370 subjects receiving PR5I and 880 in the control groups. The chance to observe at least one

specific adverse event in the PR5I group is 80% if its incidence rate is 0.05% (i.e., 1 out of every 2093 subjects), and 50% if its incidence rate is 0.02% (i.e., 1 out of every 4860 subjects). If no such adverse events are observed in the 3369 PR5I recipients, the upper limit of its incidence rate is <0.15% (i.e., 1 out of every 651 subjects).

The effect of baseline characteristics of race, ethnicity, gender, and history of premature birth ("Premature baby" and/or "Low birth weight baby" as a prior medical condition) on safety data (i.e., injection-site, systemic, serious adverse events, and elevated temperatures) were descriptively summarized by the sponsor. No statistical hypothesis tests were performed, and although there were some numerical differences noted in race and ethnicity between groups, in the opinion of the sponsor, no findings of clinical significance were associated with these baseline characteristics.

b. Pharmacovigilance Plan

For issues to be addressed by labeling, the relevant sections are indicated:

PI - Package Insert, specific section not specified

C - Contraindications Section

W - Warnings Section

PPI - patient package insert, medication guide or similar

i. Important identified safety issues: None

ii. Important potential safety issues

For the following potential safety issues, the sponsor proposes routine pharmacovigilance, reporting in Periodic Safety Update Reports (PSURs) and appropriate product labeling. NOTE: The exact wording of the label is to be determined. The comments below reflect the background and rationale provided by the sponsor with respect to these issues and are not intended to be considered as proposed labeling by either the sponsor or this reviewer.

1. Hypersensitivity including Anaphylactic reactions (C, W)

2. Febrile convulsion (C)

Infants receiving (b) (4) have an increased rate of fever $\geq 38.0^{\circ}\text{C}$, $\geq 38.5^{\circ}\text{C}$, $\geq 39.5^{\circ}\text{C}$ (49.1%, 22.9%, 2.3%, respectively) as compared to infants receiving PENTACEL (35.6%, 13.7%, 1.2%, respectively) but that this did not result in an increase in hospitalizations or other fever-related medical events.

The fever rate observed in the PR5I group (49% with temperature $\geq 38.0^{\circ}\text{C}$ after any infant dose) in Protocols 005 and 006 is similar to that reported for an EU-licensed hexavalent vaccine (INFANRIX™ hexa) administered concomitantly with pneumococcal conjugate vaccine (42 to 75%), and lower

than the rate (68%) reported for a US licensed pentavalent vaccine (PEDIARIX™) given concomitantly with 7-valent pneumococcal vaccine.

3. Hyporesponsive-Hypotonic Episodes (W)
 4. Encephalopathy/Encephalitis (C)
 5. Apnea (in premature infants less than or equal to 28 weeks gestation) (W)
 6. Extensive Limb Swelling (W)
- iii. Important missing information

Use of the product in:

1. Infants less than 6 weeks of age (PI including indication, PPI)
2. Premature infants less than 28 weeks of gestation at the time of birth.
(PI, PPI)

Note that prematurity was not an exclusionary criterion for Phase 3 studies, 2.6% of subjects had a history of prematurity. While no obvious difference in the safety profile of those with a history of prematurity and those without such a history was reported by the sponsor, detailed and specific information on prematurity was not collected nor were these subjects prospectively evaluated as a subgroup within the studies.

3. Immunocompromised patients (W, PPI)
- c. Sponsor's proposed actions and timelines
- i. Enhanced pharmacovigilance activities proposed by sponsor
Review of any identified or potential safety issues, as well as any information related to identified important missing information will be reviewed in the PSURs in the postmarket setting. Any change to the frequency and/or benefit risk profile will be discussed in the PSUR.
 - ii. Review of Postmarketing Study proposal or protocol synopsis
The sponsor is not proposing any postmarketing studies.

4. Review of other information from the Managed Review process

No additional safety concerns

5. Postlicensure Safety Review

The sponsor reports that this product is not currently licensed in any country. No epidemiological safety studies have been conducted for this product.

6. Integrated Risk Assessment

- a. There are no safety issues that would trigger a PMR or REMS.

7. Recommendations

- a. Routine pharmacovigilance with enhanced pharmacovigilance for any newly identified or potential safety issues, as proposed by the sponsor.