

Application Type	Original Application
STN	125563/0
CBER Received Date	August 12, 2014
PDUFA Goal Date	November 11, 2015
Division / Office	DVRPA /OVR
Priority Review	No
Reviewer Name(s)	Ann Schwartz, M.D.
Review Completion Date / Stamped Date	28 October 2015
Supervisory Concurrence	
Applicant	MCM Vaccine Co. [partnership between Merck Sharp & Dohme Corp. (a subsidiary of Merck and Co., Inc.) and Sanofi Pasteur Inc.]
Established Name	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine
(Proposed) Trade Name	(b) (4)
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants	Suspension for injection, each 0.5 mL dose contains: PT 20 µg FHA 20 µg FIM 5 µg PRN 3 µg Diphtheria 15 Lf Tetanus 5 Lf Vero-derived IPV-Type 1: 29 D-antigen Units Vero-derived IPV-Type 2: 7 D-antigen Units Vero-derived IPV-Type 3: 26 D-antigen Units HBsAg 10 µg PRP-OMPC 3 µg Aluminum (b) (4)
Dosing Regimen	Single intramuscular dose at 2,4 and 6 months of age
Indication(s) and Intended Population(s)	Active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), against invasive disease caused by Haemophilus influenzae type b and infection caused by all known subtypes of hepatitis B virus in children 6 weeks through 4 years of age.
Orphan Designated (Yes/No)	No

CLINICAL REVIEW FOR CR

SUMMARY

Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B [Recombinant] Vaccine is a hexavalent vaccine co-developed by Sanofi Pasteur and Merck Sharp & Dohme Corp to provide active immunization against diseases caused by *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, poliovirus types 1, 2, and 3, Haemophilus influenza type b, and hepatitis B virus when given as a three dose series. The proposed trade name is (b) (4) (DTaP-IPV-Hib-HepB), with the acronym of PR5I used to identify the investigational product in the clinical studies and this review. Components of this vaccine are currently licensed in the United States (US), the European Union (EU) and other countries. However, the combination vaccine PR5I is not currently licensed for use in any country.

This submission provides data to support the proposed indication for PR5I of active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), infection caused by hepatitis B virus, and invasive disease caused by Haemophilus influenza type b (Hib) when administered as a 3-dose series in children from 6 weeks through 4 years of age (up to the 5th birthday).

The two pivotal comparative trials (V419-005 and V419-006) submitted to support licensure under this application, both enrolled infants 46 to 89 days of age who had received one dose of monovalent hepatitis B vaccine outside of the study at birth or up to one month of age. Subjects in both studies received PR5I or PENTACEL + RECOMBIVAX HB at 2 and 6 months/PENTACEL alone at 4 months of age as a three dose infant series. Concomitant vaccination with Prevnar 13 and RotaTeq was also administered at these study visits per ACIP recommendations.

At 15 months of age, toddler vaccines were administered; with subjects in V419-005 receiving DAPTACEL, Prevnar 13 and either PedvaxHIB or ActHIB, and subjects in V419-006 receiving PENTACEL and Prevnar 13.

Adverse events were monitored after each vaccination as follows for both studies:

- Temperature (daily) Days 1-5 post-vaccination
- Solicited local injection site reactions (erythema, pain, swelling) Days 1-5 post vaccination
- Solicited systemic adverse events (crying, decreased appetite, irritability, somnolence and vomiting) Days 1-5 post vaccination
- Unsolicited adverse events for 14 days post-vaccination
- SAEs from study entry to 6 months following the toddler vaccinations at 15 months of age

The evaluation of the safety for PR5I was based upon the two pivotal studies conducted in the U.S., V419-005 (Protocol 005) and V419-006 (Protocol 006), with additional supportive safety data from two additional Phase 2 studies, V419-003 and V419-004 for the evaluation of SAEs. A total of 4265 subjects (3380 received PR5I and 885 received Control vaccines) from V419-005 and V419-006. Studies V419-003 and V419-004 (Phase 2 studies conducted in Canada) enrolled a total of 495 subjects who received the investigational vaccine formulation compared to 339 subjects in the Control groups.

In all studies, similar to what is seen following administration of the licensed component vaccines and combination vaccines containing the antigens in PR5I, common adverse events were as expected. In the pivotal studies, for PR5I post-vaccination (Day 1-5) common AEs included injection-site reactions (e.g., pain/tenderness, erythema, and swelling) and systemic adverse events such as crying, decreased appetite, irritability, pyrexia, somnolence and vomiting. A statistically significant increase in self-limited mild and moderate fever was noted for PR5I, as compared to Control vaccines in both studies. The rates of

hospitalizations and seizures related to fever was similar between the groups and generally low in incidence.

Febrile seizures rarely occur prior to 6 months of age, however, an analysis of the occurrence of increased temperature and febrile seizure during Day 1-15 following any vaccination of the infant dose of vaccine was done. No febrile seizures were noted during this time period.

The most frequently reported serious adverse event reported in the 30 days following any vaccination was respiratory syncytial virus bronchiolitis in studies V419-005 and V419-006. The majority of Serious Adverse Events that occurred during this time period in both studies were due to conditions commonly found in this age group to include gastroenteritis/dehydration, GERD, respiratory tract and other infections. 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. Death was reported for 6 subjects (0.2%) in the PR5I group and 1 subject (0.1%) in the Control group. No deaths were considered to be related to the study vaccinations (SIDS, Hydrocephalus, Sepsis, Pneumonia, Asphyxia, and Respiratory/Cardiac Arrest).

Immunogenicity of PR5I was evaluated in the pivotal Phase III, randomized, active-comparator controlled clinical trials (V419-005 and V419-006) described previously. Immunogenicity analyses were based on a per-protocol (PP) approach, excluding subjects based on certain pre-specified criteria. Two PP populations, PP-Revised Windows (PP-RW) and PP-Original Windows (PP-OW), were used in both pivotal studies. The PP-RW population allowed for more subjects to be included in the statistical analyses by extending the windows for blood draws. As pre-specified and in agreement with CBER, the success of the primary endpoints for the pivotal studies was based on the results from the PP-RW population.

For study V419-005, in infants who received 3 doses of PR5I at 2, 4, and 6 months (concomitantly with Prevnar and RotaTeq) followed by DAPTACEL and PedvaxHIB at 15 months of age, the immune responses following three doses of PR5I were non-inferior to those of the Control vaccine except for the GMT of the pertussis antigen FHA at one month post-dose 3, with a marginal miss on the non-inferiority criteria. Following the fourth dose of a DTaP vaccine, the pertussis responses of infants who had received three doses of PR5I were non-inferior to those who had received the control vaccine. The IPV response rate was 100% following the 3 dose infant series of PR5I.

The immunogenicity findings in study V419-006 (lot consistency study) were similar to those seen in V419-005 in terms of non-inferiority. Lot consistency was demonstrated with respect to GMTs and response rates for all antigens contained in PR5I. As seen in V419-005, the immune responses following three doses of PR5I were non-inferior to those of the Control vaccine except for the GMT of the pertussis antigen FHA at one month post-dose 3. After the Toddler dose, the pertussis responses and GMTs in subjects who received a 3-dose infant series of PR5I were comparable to subjects who received an infant series of a licensed Control vaccine, except for the GMT for PRN antigen which marginally missed the non-inferiority margin.

The failure to meet non-inferiority of the immune response to the pertussis FHA antigen following the infant vaccinations series in both studies is not thought to affect the clinical efficacy of PR5I to provide protection against pertussis disease.

An evaluation of immune responses following concomitant vaccination of PR5I with Prevnar 13 demonstrated immune responses that were non-inferior to those seen when Prevnar 13 was given concomitantly with the Control vaccines for 12 out of the 13 antigens, with the GMT for PCV 6B, falling outside the pre-specified immunogenicity criterion. The immune responses demonstrated to RotaTeq (concomitant vaccine) were comparable between the Control vaccine and PR5I cohorts.

Determinations regarding PR5I with respect to the Pediatric Research Equity Act (PREA) considered the availability of currently licensed vaccines which provide protection against diphtheria, tetanus, pertussis, polio, Haemophilus influenza type b and hepatitis B. PR5I as a combination vaccine that contains antigens already licensed in the US, if approved, could reduce the number of injections required at some infant visits which may increase compliance. Safety was evaluated at the same time points in the pivotal studies, with additional supportive safety data from two other studies where PR5I vaccine was administered at 15 months of age. Safety and immunogenicity data would be extrapolated for infants and toddlers through 4 years of age. The Applicant requested, for this pediatric vaccine, partial waivers based upon age groups [infants (less than 6 weeks of age) and children and adolescents (from 5 years to 17 years)]. The request was reviewed by CBER under IND 14496 as a proposed initial Pediatric Study Plan (iPSP). The request for waiver was granted under the BLA per Section 505B(a)(4)(B)(iii). The Pediatric Review Committee (PeRC) concurred with CBER's evaluation of the pediatric issues.

Currently, there are no PMCs or PMRs in place for (b) (4). Routine pharmacovigilance is planned for the product at this time.

During the review of CMC data, it was noted that some results of the (b) (4) did not meet previously established specifications during the stability testing of the pertussis toxoid contained in PR5I. (Please see CMC review). None of the lots used in the Phase 3 clinical studies, however, were out of specification at release. An Information Request letter was issued to obtain further data to address the stability of the product. Submitted (b) (4) test results indicated that lots have failed (b) (4) testing in both the real time aged product and product which was subjected to accelerated stability studies by (b) (4). This failure of the (b) (4) Tests may be indicative of (b) (4) by an interaction with the vaccine matrix, or an enhancement of the effect of the pre-existing toxin in the test by the vaccine matrix or an effect of the vaccine matrix itself on the test outcome, independent of the toxin. This failure of (b) (4) testing was also noted for lots of Quadracel and Pentacel. A Major Amendment was issued to allow the CMC reviewers to evaluate the submitted data. In the process of evaluating the data related to the (b) (4) it was noted that the data for the PRN Immunogenicity release and stability criteria for the product did not meet acceptance criteria. The requested CMC data will not be available within the review cycle for approval and is the basis upon which the CR is issued.

In conclusion, while the available safety and immunogenicity data from the pivotal studies V419-005 and V419-006 and the supportive safety data from the Phase 2 studies performed in Canada, support the licensure of (b) (4) in infants and children 6 weeks through 4 years of age, outstanding CMC issues preclude approval at this time.

2. CLINICAL AND REGULATORY BACKGROUND

PR5I has been developed jointly by Sanofi Pasteur, Ltd. and Merck Sharp & Dohme. It is manufactured using modified and/or existing bulk intermediates from vaccines currently licensed in the U.S. by Sanofi Pasteur, Ltd. or Merck & Co, Inc. (See section 2.3 Safety and Efficacy of Pharmacologically Related Products, below)

2.1 Disease to be Prevented and Available Interventions

The requested indication for PR5I is for active immunization against diphtheria, tetanus, pertussis, poliomyelitis (caused by poliovirus Types 1, 2, and 3), against invasive disease caused by Haemophilus influenzae type b and infection caused by all known subtypes of hepatitis B virus in children 6 weeks through 4 years of age. A description of each disease follows.

Diphtheria is an acute disease caused by the exotoxin-producing bacterium, *Corynebacterium diphtheriae*. In non-immune persons of all ages, symptoms of diphtheria typically occur after an incubation period of 1 to 5 days. The onset is characterized by the gradual development of a low to moderate fever and a mild, exudative pharyngitis. Transmission occurs through droplets and close physical contact, with humans being the only natural host for *C. diphtheriae*. Persons in all age groups are susceptible to diphtheria if not vaccinated. The epidemiology of diphtheria has changed dramatically, largely attributable to widespread vaccination. In the US, 147,991 cases were reported in 1920 (151 cases/100,000 population) while 5 or fewer cases have been reported annually since 1980 ($< 0.002/100,000$ population) (1). Diphtheria is a reportable disease in the U.S.

Tetanus is an infectious bacterial disease caused by environmental exposure to *Clostridium tetani*, a ubiquitous spore-forming anaerobic bacillus, which can produce a potent neurotoxin, tetanospasmin. This toxin blocks inhibitory neurotransmitters in the central nervous system and causes the muscular stiffness and spasms typical of generalized tetanus. *C. tetani* spores are ubiquitous in the environment and may be carried in the intestinal tracts of both humans and animals. Tetanus is not transmitted from person to person. The incubation period varies between 2 days and 2 months, and typically presents as trismus (lockjaw) and sudden, generalized tonic seizures. All age groups can be affected and case-fatality rates can be high even where modern intensive care is available. The overall tetanus case-fatality rate ranges from 10% to 70%, depending on treatment, age and general health of the patient. Since introduction as a component of routine childhood immunization in the 1940's, tetanus has steadily declined from as many as 600 annual cases reported nationally to 0.01 per 100,000 between the years of 2000 to 2009 (3). Tetanus is a reportable disease in the US.

Pertussis (whooping cough) is caused by the bacterium *Bordetella pertussis* and is transmitted from infected to susceptible individuals through droplets. The incubation period of pertussis ranges from 6 to 21 days (average 7 to 10 days). Early symptoms of pertussis are similar to a mild upper respiratory tract infection (catarrhal stage), and progress to cough and then to paroxysms of cough (paroxysmal stage) characterized by an inspiratory whoop commonly followed by vomiting. Fever is absent or minimal. Symptoms wane gradually over weeks to months (convalescent stage). The duration of classic pertussis is 6 to 10 weeks, in the pediatric population. Peak incidence of pertussis was in children 1 to 5 years of age: fewer than 20% of cases were in infants, and almost all children had experienced pertussis by 12 years of age. After the introduction of whole-cell pertussis vaccine in the 1940s, pertussis incidence gradually declined, from well over 100,000 cases in the US to an average of 2900 reported cases per year (approximately 1 per 100,000 population) between 1980 and 1990 (4). Since the early 1990s there has been a resurgence of pertussis in North America (5), and young infants who are not fully immunized are at highest risk among all age groups.

Poliomyelitis is an acute infectious and communicable disease caused by poliovirus, which occurs only in humans. Polioviruses are single stranded RNA enteroviruses (Picornaviridae). There are three poliovirus serotypes: 1, 2, and 3. Transmission is person-to-person via fecal-to-oral and oral-to-oral routes with an incubation period from exposure to first symptoms (minor illness) of 3 to 6 days, and from infection to onset of paralytic disease of usually 7 to 21 days, with a range of 3 to 35 days. Infection is more common in infants and young children and occurs at an earlier age among children living in poor hygienic conditions. The case fatality rate is variable and depends primarily on the age groups affected: 5 and 10% case fatality have been reported based on epidemic cases in the early 20th century. Wild-type polio is considered eradicated from the Western Hemisphere, with no wild strain-associated cases reported since 1991 although cases and outbreaks continue to be reported outside the US (8).

Haemophilus influenzae is a Gram-negative coccobacillus that enters the body through the nasopharynx. Encapsulated *Haemophilus influenzae* has 6 serological types (types a to f); however most invasive disease is caused by type b (Hib). Hib is transmitted primarily by airborne droplets or by direct contact with

respiratory secretions. Humans (asymptomatic carriers) are the only known reservoir. The invasive manifestations of Hib infection – namely, meningitis (the most common form of invasive Hib disease), pneumonia and other invasive diseases – occur primarily in infants and toddlers less than 2 years of age. The disease burden is highest among infants 4 to 18 months of age, but invasive Hib disease is occasionally observed in infants aged <3 months and among those aged >5 years. In unvaccinated populations, invasive Hib is the dominant cause of non-epidemic bacterial meningitis during the first year of life. Even with prompt and adequate antibiotic treatment, the case fatality rate of patients with Hib meningitis is 3 to 20%.

Hepatitis B infection is caused by the hepatitis B virus, a member of the hepadnaviridae family, which includes a hepatotropic group of DNA viruses. Most acute cases of hepatitis B infection in children are asymptomatic. Most patients do recover, but the chronic carrier state complicates up to 10% of cases acquired in adulthood. The rate of acquisition of chronic infection depends largely on the mode and age of acquisition and is up to 90% in perinatal cases. Chronic hepatitis cirrhosis and hepatocellular carcinoma are seen with chronic infection.

For children in this age group, 6 weeks through 4 years of age, the following component and combination vaccines are licensed in the U.S. for prevention of diseases targeted by PR5I (See also Section 2.3 of this review) :

- DTaP
 - DAPTACEL (Sanofi Pasteur, Ltd.)
 - Tripedia (Sanofi Pasteur Inc.)
 - INFANRIX (GlaxoSmithKline)
- Diphtheria and Tetanus Toxoids Adsorbed for Pediatric Use (DT)
 - DT, Sanofi Pasteur Inc. and Sanofi Pasteur Limited
- Hib conjugate vaccine
 - ActHIB
 - PEDVAXHIB (Meningococcal Protein Conjugate; Merck)
 - Hiberix (GlaxoSmithKline) (as a booster dose only)
- Poliovirus Vaccine Inactivated (IPV)
 - IPOL (Sanofi Pasteur Inc.)
 - POLIOVAX (Sanofi Pasteur Limited; not distributed in the U.S.)
- DTaP, Hepatitis B (Recombinant) and IPV Combined
 - PEDIARIX (GlaxoSmithKline)
- DTaP and IPV Combined
 - KINRIX (GlaxoSmithKline)
 - QUADRACEL (Sanofi Pasteur, Limited)
- DTaP, IPV, and Hib conjugate Combined
 - PENTACEL (Sanofi Pasteur, Ltd)
- Hib conjugate and hepatitis B (recombinant) vaccine
 - COMVAX (Merck)
- ActHIB reconstituted with Tripedia
 - TriHIBit, Sanofi Pasteur Inc. (for use in children 15-18 months of age only)
- Hepatitis B
 - Recombivax HB (Merck & Co, Inc)
 - Engerix-B (GlaxoSmithKline Biologicals)

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

In general, the treatment for each of the diseases described in section 2.1 is supportive in nature.

2.3 Safety and Efficacy of Pharmacologically Related Products

The components of the PR5I vaccine are currently licensed and distributed in the U.S. either as stand-alone vaccines or as part of combination vaccines. (Please see section 6.1.4 of this review for a description of the products.) Safety and efficacy of these products has been previously evaluated and are summarized in current product packaging inserts for the noted products.

The components of the PR5I Vaccine and related products are presented below:

P- PRP-OMPC Bulk Intermediate, from Liquid PedvaxHIB® (STN BL 103237)
[Haemophilus influenza type b Conjugate Vaccine (Meningococcal Protein Conjugate)]
– Merck, Sharp and Dohme, Corp.

R- Hepatitis B Surface Antigen (HBsAg) Bulk Intermediate (also described as HBsAg Bulk Intermediate), from RECOMBIVAX HB® (STN BL 101066) [Hepatitis B Vaccine (Recombinant)] – Merck, Sharp and Dohme, Corp.

5- Five component Acellular Pertussis Adsorbed (Pertussis Toxoid, Filamentous Haemagglutinin, Pertactin, and Fimbriae Types 2 and 3), Diphtheria Toxoid Adsorbed and Tetanus Toxoid Adsorbed Bulk Intermediates. These antigens are used in other US licensed products including, Pentacel® (STN BL 125145), Diphtheria and Tetanus Toxoids Adsorbed Vaccine (STN BL 103944), DAPTACEL® (STN BL 103666), Adacel® (STN BL 125111) and TENIVAC™ (STN BL 103171) – Sanofi Pasteur Limited

I- Inactivated Poliovirus Types 1, 2, and 3 Bulk Intermediate [Poliovirus Vaccine Inactivated], these antigens are used in other US licensed products, including IPOL® (STN BL 103930) – Sanofi Pasteur SA (vIPV)

Of note, the polio antigens for (b) (4) /PR5I [DTaP-IPV-Hib-HepB] are produced in Vero cells, whereas the polio antigens contained in Pentacel [DTaP-IPV-Hib] vaccine are produce in MRC5 cells.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

This vaccine is not currently licensed in the U.S. or outside of the U.S.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

- Initial studies during the clinical development of PR5I were not conducted under US Investigational New Drug (IND) submission. The phase 1 and 2 studies (V419-001, V419-002, V419-003, and V419-004) assessed the safety and immunogenicity of four related investigational hexavalent vaccine formulations, varying in dose and formulation, in infants and toddlers under Canadian Health Authority applications. This phase 1/2 program was completed in June 2008.
- End-of-phase 2/Pre-IND Meetings were held with CBER on March 28, 2007, and on January 25, 2008, to discuss the Phase III chemistry, manufacturing, and clinical development plan for PR5I.
- An Investigational New Drug Application (IND) was submitted to CBER under BB-IND 14496 on September 21, 2010. The phase 3 clinical development plan included 4 immunogenicity and safety studies as follows:
 - Two studies (V419- 005 and V419-006) conducted in the United States under IND 14496 were intended to assess the safety, tolerability, and immunogenicity of PR5I when administered concomitantly with licensed pediatric vaccines, and to serve as the pivotal studies for the U.S. licensure. A total of 3380 subjects received at least one dose of PR5I in the U.S. studies.

- Two studies (Protocol 007 and Protocol 008) were conducted in the European Union (EU) to assess the safety, tolerability, and immunogenicity of PR5I when administered concomitantly with licensed pediatric vaccines using EU vaccination schedules. The data from these EU-based studies are intended to support licensure of PR5I in the EU. Initially, the sponsor indicated that these two EU studies would not be submitted as part of the US licensure application. However, CBER requested that the safety data from the EU studies be submitted as information only (not in support of US licensure).
- On June 27, 2013, Sanofi Pasteur submitted a Type C Meeting Request to obtain CBER concurrence on the Chemistry, Manufacturing and Control (CMC) aspects of the license application for PR5I vaccine. In lieu of a meeting, a written response was sent to the sponsor on September 11, 2013 by fax. The Type B (pre-BLA) meeting, which was to gain CBER concurrence on the adequacy of the clinical safety and immunogenicity profile of PR5I to support U.S. licensure and the plan for the timing of submission of certain additional stability data, was held on April 25, 2014.
- An informal initial Pediatric Study Plan (iPSP) for PR5I vaccine was submitted by Sanofi Pasteur Limited for CBER comment on March 6, 2014. Based on CBER comments on the informal iPSP dated April 8, 2014, Sanofi Pasteur Limited submitted the formal iPSP as an amendment to their IND 14496 on April 17, 2014. The Pediatric Equity Research Committee (PeRC) reviewed the iPSP on June 18, 2014. On June 19, 2014, CBER communicated the PeRC review comments to Sanofi Pasteur Limited and requested the submission of an 'Agreed PSP.' Sanofi Pasteur Limited submitted 'Agreed PSP' on June 20, 2014, which was approved in the PeRC meeting on July 16, 2014. The Agreed PSP was included in the BLA, STN 125563/0.
- The biologics license application (BLA) for PR5I was submitted on August 12, 2014 with the proposed indication of active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* type b as a three dose series in children from 6 weeks through 4 years of age. The vaccine is manufactured for MCM Vaccine Company, a joint venture between Merck and Sanofi Pasteur Limited. The BLA was initially submitted under Sanofi's current license, subsequently changed the applicant to MCM Vaccine Company and a new license number has been issued. Sanofi Pasteur Limited will manufacture DTaP, Sanofi Pasteur SA will manufacture IPV, and Sanofi Pasteur Limited will manufacture the final drug product. Merck will manufacture Hib and HepB, and provide these bulk intermediates to Sanofi. Sanofi Pasteur Inc. will be responsible for submitting information for MCM Vaccine Company. Merck submitted two For Further Manufacturing Use (FFMU) BLAs STN125580/0 (PedvaxHiB, Hib) and STN125581/0 (Recombivax HB, HepB) including information regarding the manufacture of the bulk intermediates. The FFMU BLAs are cross referenced to the BLA.
- Multiple amendments have been submitted to the file and to other related files [Sanofi Pasteur] to address several outstanding issues related to Chemistry, Manufacturing and Control of the investigational product for licensure.
- The submission of CMC data on 25 June 2015 to the file was deemed to be a major amendment and the review clock was extended to 11 November 2015. The Applicant was notified of this decision on 06 July 2015.

2.6 Other Relevant Background Information

As noted in Section 2.5 above, Sanofi Pasteur Inc. and Merck Sharpe and Dome Corporation (subsidiary of Merck & Co., Inc) have entered into a shared manufacturing agreement as MCM Vaccine Company to have oversight of the development, manufacture, and release of PR5I (proposed trade name (b) (4)). Sanofi Pasteur Inc. will be responsible for publishing of the BLA and submissions to FDA on behalf of MCM Vaccine Co. MCM Vaccine Co., will have responsibility for post approval obligations, such as post marketing clinical trials, additional product stability studies, complaint handling, recalls, post market

reporting as required under 21 CFR 601.12. MCM Vaccine Co. will also have responsibility for adverse experience reporting.

As per the Cooperative Manufacturing guidance (Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics, November, 2008), MCM Vaccine Co. is eligible to be the applicant for the Biologics License for PR5I because it had oversight for vaccine development of PR5I and will also have responsibility for commercial manufacturing of the drug product (formulation, filling, and packaging) by Sanofi Pasteur Limited (Ontario, Canada), which operates as (b) (4) (Contract Manufacturing Organization) for MCM Vaccine Co. There is a shared manufacturing arrangement between the MCM Vaccine Co. and the partner companies supplying the drug substances, Merck Sharp & Dohme Corp (Haemophilus b conjugate and Hepatitis B Surface Antigen) and Sanofi Pasteur Inc. (supplier of Tetanus Toxoid Adsorbed, Diphtheria Toxoid Adsorbed, 5-Component Acellular Pertussis Adsorbed, and Inactivated Vero Trivalent Polio vaccine bulk) to manufacture PR5I. The drug substances are components of vaccines that are currently licensed in United States, as outlined in the table below.

Table 1. STN 125636: Drug Substance used in manufacturing of PR5I

Drug Substance used in manufacturing of PR5I	US Licensed product(s) that contains drug substance components	Application #
Tetanus Toxoid Adsorbed	Pentacel [®] (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus (MRC-5) and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine /Sanofi Pasteur, Inc.	STN 125145
Diphtheria Toxoid Adsorbed	Pentacel [®] (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus (MRC-5) and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine /Sanofi Pasteur, Inc.	STN 125145
5-Component Acellular Pertussis Adsorbed which is composed of five antigens (Fimbriae Types 2 and 3 (FIM) Adsorbed, Pertactin (PRN) Adsorbed, Pertussis Toxoid (PT) Adsorbed, Filamentous Haemagglutinin (FHA) Adsorbed)	Pentacel [®] (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus (MRC-5) and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine /Sanofi Pasteur, Inc.	STN 125145
Inactivated Vero Trivalent Polio vaccine bulk (vIPV)	IPOL [®] (Poliovirus Vaccine Inactivated)/ Sanofi Pasteur, Inc.	STN 103930
Haemophilus b conjugate (PRP-OMPC)	PedvaxHIB [®] Liquid [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]/ Merck Sharp & Dohme Corp	STN 103237

Drug Substance used in manufacturing of PR5I	US Licensed product(s) that contains drug substance components	Application #
Hepatitis B Surface Antigen (HBsAg)	RECOMBIVAX HB [®] [Hepatitis B Vaccine (Recombinant)]/ Merck Sharp & Dohme Corp	STN 101066

Source: STN 125563/0.4 (date 04 November 2014), Section 1.11.1, pages 3.

Of note, information regarding many of the CMC issues related to the final product has been submitted under related INDs held by Sanofi Pasteur alone due to proprietary concerns. The CMC data has been reviewed under these respective files.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

The primary source of data considered for review of this investigational product were documents submitted under STN 125563/0 and amendments to the file. Supportive information on the clinical study protocols was reviewed and referenced under BB IND 14496.

Studies contained under section 5.3.5.1 of the original submission and the presentation of integrated summaries of safety and effectiveness in section 5.3.5.3 were the primary source documents.

Draft labeling was submitted under amendment 4 to the BLA indicating merger status of Merck and SP for product manufacturing and distribution.

Concurrent memos from other review team members were consulted.

The following sections were reviewed in support of this application:

Section 5.3.5.1 Final Study Clinical Study Reports

Section 1.9.4 Proposed Pediatric Study Request

Section 1.14.1 Draft Labeling (under amendment 4 to the BLA)

Section 1.16.1 Pharmacovigilance plans

Section 2.5 Clinical Overview

Section 2.7.3 Summary of Clinical Efficacy

Section 2.7.4 Summary of Clinical Safety

Section 5.2 Tabular Listing of all Clinical studies

3.2 Compliance with Good Clinical Practices and Submission Integrity

Bioresearch Monitoring inspections of six clinical site were conducted in support of this Biologics Licensing Application (BLA). Inspections of these clinical investigators did not reveal significant problems that impact the data submitted in this BLA. Two sites for study V419-005, enrolling 1473 subjects at 39 United States sites were selected and represented ~9% of enrolled subjects. For study V419-006, 2808 subjects were enrolled at 73 study centers within the United States. Four sites were selected for BIMO inspection, representing ~10% of the enrolled subjects.

One site for V419-006 (Layton, Utah) was issued a Form FDA 483. The FDA Form 483 listed at least 14 subjects' adverse event data from the diaries were missing or incorrectly transcribed into the case report forms. This inspection was classified as VAI (Voluntary Action Indicated).

4 TABLES OF STUDIES/CLINICAL TRIALS

Table 2. STN 125636: Primary Studies for Licensure PR5I (V419)

	005	006 (lot consistency)	Total subjects planned
Number of subjects planned for enrollment (enrolled)	1440 (1465)	2800 (2808)	4200
Number of subjects to receive PR5I planned (Enrolled and vaccinated)	960 (981)	2400 (2232)	3660
Subjects to receive active Control vaccines planned (enrolled and vaccinated)	480* (484)	400^ (370)	880
Randomization	2:1	2:2:2:1	-
Timing of doses of PR5I administered	2,4,6 months	2,4,6 months	-
Concomitant vaccines months 2,4,6	Prevnam 13, RotaTeq	Prevnam 13, RotaTeq	-
Birth dose monovalent Hepatitis B vaccine	yes	yes	-
Fourth dose in series (15 months)	Daptacel, PedvaxHib, Prevnam 13	Pentacel, Prevnam 13	-
Duration	~ 14 months	~ 14 months	-

Reviewer generated table.

*PENTACEL at months 2, 4 and 6 and Recombivax HB¹ at months 2 and 6, followed by Daptacel, Prevnam 13 and ActHIB at month 15

^PENTACEL at months 2, 4 and 6 and Recombivax HB¹ at months 2 and 6, followed by Pentacel and Prevnam 13 at month 15
1 Recombivax HB intended for use in Study V419-005 and -006 manufactured according to an investigational, modified process using (b) (4)

Table 3. STN 125636: Supportive Safety Studies for Licensure PR5I (V419)

Protocol 003	Partially Double-Blind, Randomized, Controlled, Dose-Ranging, Multicenter Study to Evaluate the Safety, Tolerability, and Immunogenicity of 3 Different Formulations of HR5I	756 male and female healthy hepatitis B vaccine-naïve infants, 2 months of age
Protocol 004 [PR504]	A Randomized Trial to Assess the Immunogenicity and Safety of (b) (4) to the Hepatitis B Component and When Given Concomitantly With Prevnam TM	460 male and female healthy hepatitis B vaccine-naïve infants, 42 to 89 days of age

5 Recommendations on Regulatory Actions

The safety and immunogenicity data in the BLA support a recommendation for approval of (b) (4) (PR5I) in infants and children, 6 weeks through 4 years of age (prior to the fifth birthday) for active immunization against invasive Hib disease, diphtheria, tetanus, pertussis, hepatitis B and poliomyelitis. The dosage regimen supported by clinical data is a single 0.5 mL dose of (b) (4) administered by the intramuscular route, at 2, 4, and 6 months of age.

However, the outstanding CMC issues pertaining to the stability and manufacture of (b) (4) preclude approval of (b) (4) at this time. Pending satisfactory resolution of these issues, a recommendation for approval based on the review of the submitted clinical data submitted may be indicated.

(b) (4) contains the same components of products already licensed in the U.S. for active immunization against diphtheria, tetanus, pertussis, hepatitis B, haemophilus influenza B and polio. This vaccine

represents a convenience vaccine which could reduce the number of injections at a clinical visit when compared to administration of separate licensed vaccines for the same indication. Due to the availability of other licensed products to prevent the diseases caused by diphtheria, tetanus, pertussis and Haemophilus influenza bacteria and hepatitis B and polio viruses (see sections 2.1 and 2.3 above), there will be no unmet medical need due to this regulatory action.