U.S. FOOD & DRUG ADMINISTRATION

January 21, 2021

Elizabeth A. Brehm, Esq.
Informed Consent Action Network
200 Park Avenue, 17th Floor
New York, NY 10166

In reply refer to file: 2020-8193 (IR#0367)

Dear Ms. Brehm,

This is in reply to your Freedom of Information Act request dated November 16, 2020, in which you requested " "Summary Basis for Regulatory Action" OR "Summary Basis of Approval" OR equivalent document, dated in or around 1989/1990 for the Pedvax HIB vaccine." Your request was received in the Center for Biologics Evaluation and Research on November 18, 2020.

Enclosed is a Summary for Basis of Approval for PedvaxHIB that is responsive to your request. Please note that as these records have previously been disclosed, no review charges have been assessed.

We have withheld portions of pages under Exemption (b)(4), 5 U.S.C. § 522(b)(4). That exemption permits the withholding of trade secrets and commercial or financial information that was obtained from a person outside the government and that is privileged or confidential.

You have the right to appeal this determination. By filing an appeal, you preserve your rights under FOIA and give the agency a chance to review and reconsider your request and the agency's decision.

Your appeal must be mailed within 90 days from the date of this response, to:

Director, Office of the Executive Secretariat
US Food & Drug Administration
5630 Fishers Lane, Room 1050
Rockville, MD 20857
E-mail: FDAFOIA@fda.hhs.gov

Please clearly mark both the envelope and your letter "FDA Freedom of Information Act Appeal."

If you would like to discuss our response before filing an appeal to attempt to resolve your dispute without going through the appeals process, please contact Beth Brockner Ryan at 240-402-8026.

You also have the right to contact the Office of Government Information Services (OGIS). The Federal FOIA Ombudsman's office offers mediation services to help resolve disputes between FOIA requesters and Federal agencies.

The contact information for OGIS is:

Office of Government Information Services
National Archives and Records Administration
8601 Adelphi Road–OGIS
College Park, MD 20740-6001
Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-mail: ogis@nara.gov
Fax: 202-741-5769

If you have any questions or if we can be of further assistance, please let us know by referencing the above file number. You can contact Elizabeth Sly by phone at 240-402-8001 or by e-mail at Elizabeth.Sly@fda.hhs.gov.

Sincerely,

Beth A. Brockner Ryan -S

Digitally signed by Beth A. Brockner Ryan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300052489, cn=Beth A. Brockner Ryan -S
Date: 2021.01.21 14:17:56 -05'00'

Beth Brockner Ryan
Chief, Access Litigation and Freedom of Information Branch

[Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate, MSD)]
Summary for Basis of Approval

Reference No.: 90-0511

Drug Licensed Name
Haemophilus b Conjugate Vaccine
(Meningococcal Protein Conjugate)

Manufacturer:
Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
West Point, PA 19486

Drug Trade Name:
PedvaxHIB™

PedvaxHIB™ [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate, MSD)] is composed of a highly purified capsular polysaccharide (polyribosylribitol phosphate or PRP) of Haemophilus influenzae type b (Haemophilus b, Ross strain) covalently bound to an outer membrane protein complex (OMPC) of the B11 strain of Neisseria meningitidis serogroup B.

I. INDICATIONS FOR USE

PedvaxHIB™ is indicated for routine immunization against invasive disease caused by Haemophilus influenzae type b in infants and children 2 to 71 months of age. The vaccine has been shown to be effective in inducing an immune response (anti-PRP) in infants as young as 6 weeks of age. It has also been shown to be highly effective in preventing invasive Haemophilus b infection among Native American (Navajo) infants who are at increased risk for disease with evidence of protection beginning after a single dose of vaccine.

As with other vaccines, several days following administration of PedvaxHIB™ are required for protective antibody levels to be achieved.

PedvaxHIB™ will not protect against Haemophilus influenzae other than type b or against other microorganisms that cause meningitis or sepsis.

No impairment of immune response to the individual tested vaccine antigens was demonstrated when PedvaxHIB™ was administered concomitantly at separate sites with Measles, Mumps and Rubella Virus Vaccine (M-M-R®$_{II}$) or Diphtheria and Tetanus Toxoid and Pertussis (DTP) Vaccine and Oral Polio Virus (OPV) Vaccine.

II. DOSAGE AND ADMINISTRATION

The vaccine is a lyophilized preparation containing lactose as a stabilizer. It is reconstituted with an aluminum hydroxide diluent containing thimerosal (a mercury derivative) as a preservative. Each 0.5 ml dose of the vaccine when reconstituted as directed contains 15 mcg of Haemophilus b PRP, 250 mg of Neisseria meningitidis OMPC, 225 mcg of aluminum as aluminum hydroxide, thimerosal at 1/20,000, and 2.0 mg of lactose, in 0.9% sodium chloride. PedvaxHIB™ is supplied as a single dose vial of lyophilized vaccine and a vial of aluminum hydroxide diluent.

Vaccination consists of a single 0.5 ml injection of vaccine for children 15 months of age and older or two 0.5 ml primary injections given 2 months apart for infants and young children 2 to 14 months of age. When the primary two-dose regimen is initiated at 2 to 10 months of age, a booster dose is recommended at 12 to 15 months of age. When reconstituted as directed each injection of vaccine contains 15 mcg (0.5 ml) of Haemophilus influenzae type b capsular polysaccharide. All injections are given intramuscularly into the anterolateral thigh or the outer aspect of the upper arm.

III. MANUFACTURING AND CONTROLS

A. Manufacturing and Control Testing

The product is a bacterial vaccine consisting of the purified capsular polysaccharide, polyribosylribitol phosphate (PRP) from Haemophilus influenzae type b (Ross strain) that is covalently bound to a vesicular outer membrane protein complex (OMPC) from the B11 strain of Neisseria meningitidis. The covalent bonding between the PRP and the OMPC provides enhanced immunogenicity of the PRP in infants and young children.

H. influenzae type b seed is inoculated into a production fermenter containing a complete Haemophilus medium ([redacted] After incubation the H. influenzae b culture is inactivated by the addition of [redacted]. The bacterial cells in the culture [redacted] are concentrated by [redacted].

The PRP is isolated to a high degree of purity using a [redacted] phenol extraction[redacted] and selective ethanol [redacted] to remove bacterial cellular components and medium components.

A. Manufacturing and Control Testing (Cont.)

The purified PRP contains ≤1.0% nucleic acid, ≤1.0% protein and passes the rabbit pyrogen test at 1 mcg/mL/kg.

The N. meningitidis B_{11} is cultured in a complete Neisseria medium [redacted] medium supplemented with [redacted] and is inactivated after the fermentation is completed by the addition of [redacted]. The [redacted] cell concentrate is then treated with a detergent to extract OMPC. Cell debris is removed by [redacted] The OMPC extract is [redacted] and further purified through [redacted] centrifugation: [redacted]. The OMPC is sterilized by membrane filter and diafiltered with [redacted] The N. meningitidis protein [redacted] contains ≤1.5% nucleic acids, [redacted] neutral sugars, and passes the rabbit pyrogen tests at ≥0.25 mcg/mL/kg.

The OMPC is activated by the addition of a terminal thiol group and the PRP is activated by the addition of a terminal bromo acetyl group. The chemistry of the conjugation involves nucleophilic displacement of the bromide (from the bromoacetamide group) by the thiol resulting in a thioether bond which is the covalent linkage between the PRP and the OMPC. [redacted] and [redacted] are used to purify the conjugate product.

The conjugated product is diluted with water to a target concentration of 30 mcg/ml of PRP, and lactose is added to a concentration of 2 to 5 mg/ml.

The final vaccine is a lyophilized product and is tested for general safety, sterility, identity, pyrogenicity (IV and IM), immunogenicity in mice, and content of PRP.

Three lots of vaccine (42595, 42596 and 42597) were submitted to demonstrate manufacturing consistency. These consistency lots were tested and met approved specifications.

B. Stability Studies

The recommended storage temperature for the vaccine is 2 to 8°C. Stability of the vaccine was monitored at the recommended storage temperature by measuring free ribose, conjugated polysaccharide antigen following chromatographic separation, total polysaccharide antigen, mouse immunogenicity, and immunogenicity in infant Rhesus monkeys. No detectable loss of potency or physical integrity was observed by any of the methods or tests used throughout the [redacted] study.

B. Stability Studies (Cont.)

These results, as well as results from studies at elevated temperature form the basis for the recommended dating period of 18 months.

D. Labeling

The primary label used on the vials of Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) states: the proper name and the trade name, PedvaxHIB™; vial size and volume; a caution stating "NOT FOR INTRAVENOUS USE"; a caution stating "SHAKE WELL AFTER RECONSTITUTION"; the Durham-Humphrey statement; a space for adding a lot number and expiration date at the time of packaging; a space for the component number; the applicant's name and address "Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486, USA; and U.S. Govt. Lic. No. 2.

The primary label used on the vials of Aluminum Hydroxide Diluent state: the proper name, the vial size and volume; the product number; a caution stating "NOT FOR INTRAVENOUS USE"; a caution stating "SHAKE WELL BEFORE USE"; The Durham-Humphrey statement; a space for adding a lot number and expiration date at the time of packaging; and the applicant's name and address "Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486, USA.

The carton containing 1 vial of vaccine and 1 vial of diluent for Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) states: the proper name and the trade name, PedvaxHIB™; the vaccine vial size and volume; a statement referring to the package insert for dosage information; ingredient statement for the vaccine and the diluent; storage conditions; the Durham-Humphrey statement; a caution against intravenous use; a caution to shake the diluent and the reconstituted vaccine before use; a caution to use only the diluent supplied for reconstitution of the vaccine; the product number; a space for the component number; a space for adding a lot number and expiration date at the time of packaging; the NDC number; the applicant's name and address "Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486, USA; U.S. Govt. Lic. No. 2; and U.S. Patient 4,694,624.

D. Labeling (Cont.)

The carton containing 5 vials of vaccine and 5 vials of diluent for Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) states: the proper name and the trade name, PedvaxHIB™; the color codes for the vaccine and the diluent; the vaccine vial size and volume; a statement referring to the package insert for dosage information; ingredient statement for the vaccine and the diluent; storage conditions; the Durham-Humphrey statement; a caution against intravenous use; a caution to shake the diluent and the reconstituted vaccine before use; a caution to use only the diluent supplied for reconstitution of the vaccine; the product number; a space for the component number; a space for adding a lot number and expiration date at the time of packaging; the NDC number; the applicant's name and address "Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486, USA; U.S. Govt. Lic. No. 2; and U.S. Patient 4,695,624.

The package insert (copy attached) contains statements regarding description, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, dosage and administration, how supplied, and information on the storage of the vaccine.

V. MEDICAL

A. General Information

Haemophilus influenzae type b (Haemophilus b) is the most frequent cause of bacterial meningitis and a leading cause of serious, systemic bacterial disease in young children worldwide.

Haemophilus b disease occurs primarily in children under 5 years of age and in the United States accounts for nearly 20,000 cases of invasive infections annually, approximately 12,000 of which are meningitis. The mortality rate from Haemophilus b meningitis is about 5%. In addition, up to 35% of survivors develop neurologic sequelae including seizures, deafness, and mental retardation. Other invasive diseases caused by this bacterium include cellulitis, epiglottitis, sepsis, pneumonia, septic arthritis, osteomyelitis and pericarditis.

The peak incidence of Haemophilus b meningitis occurs between 6 to 11 months of age. Forty-seven percent of all cases occur by one year of age with the remaining 53% of cases occurring over the next 4 years.

A. General Information (Cont.)

Among children under 5 years of age, the risk of invasive Haemophilus b disease is further increased in certain populations including daycare attendees, lower socio-economic groups, blacks (especially those who lack the Km(1) immunoglobulin allotype), caucasians who lack the G2m (n or 23) immunoglobulin allotype, Native Americans, household contacts of cases, and individuals with asplenia, sickle cell disease, or antibody deficiency syndromes.

An important virulence factor of the Haemophilus b bacterium is its polysaccharide capsule (PRP). Antibody to PRP (anti-PRP) has been shown to correlate with protection against Haemophilus b disease. While the anti-PRP level associated with protection using conjugated vaccines has not yet been determined, the level of anti-PRP associated with protection in studies using bacterial polysaccharide immune globulin or nonconjugated PRP vaccines ranged from $\geq$0.15 to $\geq$1.0 mcg/ml.

Nonconjugated PRP vaccines are capable of stimulating B-lymphocytes to produce antibody without the help of T-lymphocytes (T-independent). The responses to many other antigens are augmented by helper T-lymphocytes (T-dependent). PedvaxHIB™ is a PRP-conjugate vaccine in which the PRP is covalently bound to the OMPC carrier producing an antigen which is postulated to convert the T-independent antigen (PRP alone) into a T-dependent antigen which results in both an enhanced antibody response and immunologic memory.

B. Clinical Studies

Clinical trials were conducted to evaluate the safety and immunogenicity of PedvaxHIB™ in infants and children 2 months of age and older.

Subjects 12 months of age and older received a single injection of vaccine; infants and young children under 12 months of age and a subset of children 12 to 17 months of age received two primary injections given two months apart. A booster injection was administered at 12 to 18 months of age in a subset of subjects. The vaccine was administered by intramuscular injection into the anterior thigh or deltoid region. Administration of other vaccines was deferred for a week or longer.

B. Clinical Studies (Cont.)

Vaccinees were observed for immediate reactions during the first 15 minutes postvaccination. Thereafter, parents recorded temperatures, reactions at the injection site and systemic sequelae for 3 to 5 days by means of a standardized vaccination card. Observations for serious adverse reactions were continued for 14 days.

Serum samples were obtained and stored frozen prior to each, and one month after the last vaccination. Anti-PRP antibody was determined by a Farr-type standardized radioimmunoassay that utilized extrinsically labelled [I^{125}]-PRP. The lower limit of sensitivity of the assay was 0.125 mcg/ml.

1. Safety

Over 8086 doses of PedvaxHIB™ have been administered to 5027 subjects in clinical trials evaluating immunogenicity and safety. PedvaxHIB™ was generally well tolerated in all age groups after each dose. No vaccine-related adverse events were reported. In a subset of subjects evaluated for fever and injection site reactions over a two-day period, reactions of clinical significance were infrequent (Table 1). No pattern of increasing reactions was noted over the 48 hours of observation and a second injection was not associated with increased reactions. Injection site and systemic reactions reported in >1% frequency are summarized in Table 2. As with local reactions, systemic reactions did not increase with revaccination.

The tolerability of PedvaxHIB™ was assessed when administered concurrently with other vaccines (measles, mumps, rubella virus vaccine, diphtheria and tetanus toxoids and pertussis vaccine and oral polio virus vaccine) and compared with reactions reported when the other vaccines were administered without PedvaxHIB™. No significant increase in adverse events were reported in the group administered PedvaxHIB™ in addition to the other vaccines at separate sites.

In a protective efficacy study, approximately 5000 healthy Navajo infants 6 to 12 weeks of age received PedvaxHIB™ or placebo. Most of these infants received DTP/OPV concomitantly. In a subset of 4459 infants, no differences were seen in the type and frequency of serious adverse experiences reported among those who received PedvaxHIB™ and those who received placebo, and none was reported to be related to PedvaxHIB™. Only one serious reaction (tracheitis)

B. Clinical Studies (Cont.)

was reported as possibly related to PedvaxHIB™ and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups and were not reported to be related to PedvaxHIB™. The frequencies of fever and injection site reactions occurring in a subset of these infants during a 48-hour period following each dose were similar to those seen in other clinical studies (Table 1).

2. Immunogenicity

PedvaxHIB™ was highly immunogenic in all age groups evaluated. A significant and consistent antibody response was seen after a single dose of vaccine in all age groups including infants as young as 2 months of age. After the recommended number of doses 99% and 91% of infants 2 to 71 months of age responded with >0.15 mcg/ml anti-PRP and >1.0 mcg/ml anti-PRP, respectively. Among subjects who received two doses of PedvaxHIB™, 98% and 75% achieved antibody levels >0.15 mcg/ml and >1.0 mcg/ml, respectively, after the first dose. Pre- and postvaccination anti-PRP geometric mean titers (GMTs) of subjects by age groups, and proportions with ≥0.15 mcg/ml and >1.0 mcg/ml antibody levels are summarized in Table 3. Antibody response was characterized by the following features: (1) consistent rise in antibody after the first dose of vaccine in all groups of subjects down to two months of age; (2) further increase in antibody following administration of second dose of vaccine; (3) higher antibody levels among older subjects. When three different lots of vaccine were evaluated in a randomized fashion among a subset of subjects, no differences in antibody response was observed among the lots, confirming vaccine lot-to-lot consistency. Immune responses to individual tested antigens were not impaired when PedvaxHIB™ was administered concomitantly with either measles, mumps and rubella virus vaccine or diphtheria and tetanus toxoid and pertussis vaccine and oral polio virus vaccine.

Anti-PRP levels decline at a similar rate among all age groups studied. A booster immunization at ≥12 months of age results in significantly increased antibody levels possibly adequate to protect children for the rest of the at-risk period for Haemophilus b disease. The persistence of antibody and the booster effect of revaccination is shown by age group in Table 4. Among infants in the 2 to 3 month age group, revaccination at 12 to 17 months resulted in a 26.9-fold

B. Clinical Studies (Cont.)

rise in anti-PRP GMT. Infants in the 4 to 11 month age group also demonstrated impressive rises in antibody levels following revaccination.

Anti-PRP antibodies induced by PedvaxHIB™ are predominantly of IgG isotype across all age groups. Similarly, all age groups developed IgG_1 subclass antibodies but only ≥18 month old subjects showed substantial levels of IgG_2 subclass antibodies.

Vaccine-induced antibodies demonstrated biological activities exemplified by *in vitro* assays for *Haemophilus influenzae* type b bacteriolysis and opsonophagocytosis and an *in vivo* test in an infant rat model for protecting against experimentally induced Hib infection.

3. Efficacy

The protective efficacy of PedvaxHIB™ has been demonstrated in a randomized double-blind, placebo-controlled study in approximately 5000 Native American (Navajo) infants. This population has the highest incidence of Haemophilus b disease in the United States, a peak incidence occurring earlier in infancy, and also has a lower antibody response to conjugated Haemophilus b vaccines, including PedvaxHIB™. Therefore, demonstration of efficacy in such a high risk population would be expected to be predictive of efficacy in other populations.

In this study, efficacy in prevention of invasive Haemophilus b disease was 93% (p=0.0010) in 3,486 infants who received the recommended two-dose regimen of PedvaxHIB™. Twenty-two cases of invasive Haemophilus b disease occurred in the placebo group (8 cases after the first dose and 14 cases after the second dose) and only 1 case in the vaccine group (none after the first dose and 1 after the second dose). Following the first dose, the difference in number of cases of disease between placebo and vaccine recipients was statistically significant (p=0.0078), indicating that protection began after the first dose.

TABLE 1

Percentage of Vaccinees with Fever or Injection Site Reactions
Following Immunization With PedvaxHIB™

		Dose 1				Dose 2			
Age (Mos)	Reaction	No. of Subjects Evaluated	6 Hr.	24 Hr.	48 Hr.	No. of Subjects Evaluated	6 Hr.	24 Hr.	48 Hr.
2-14	Fever >38.3°C (101°F)	989	1.0	1.5	0.9	564	1.3	1.5	1.8
	Swelling >1 inch diameter/ Induration	1026	0.6	1.5	1.6	585	0.9	2.8	3.7
	Erythema >1 inch diameter	1026	0.2	1.0	0.4	585	0.9	1.2	0.7
15-71	Fever >38.3°C (101°F)	531	2.6	1.7	2.0	—	—	—	—
	Swelling >1 inch diameter/ Induration	572	0.9	2.1	1.4	—	—	—	—
	Erythema >1 inch diameter	572	0.0	0.3	0.2	—	—	—	—

TABLE 2

Incidence of Clinical Reactions Reported in Infants 2 to 71 Months of Age During the 48 Hours Following Immunization with PedvaxHIB™

	Incidence (%)	
	Dose 1 (n=790)	Dose 2 (n=584)
Injection Site Reactions		
Swelling ≤1 inch	12.0	14.7
Erythema ≤1 inch	18.1	17.5
Swelling >1 inch/Induration	1.9	4.5
Erythema >1 inch	1.3	1.5
Pain/Soreness	7.8	9.1
Systemic Reactions		
Irritability	27.3	25.0
Sleepiness/Lethargy	21.4	15.4
Warm to Touch	12.7	11.6
Diarrhea/Vomiting/Nausea	9.9	7.0
Crying	6.3	3.1
Respiratory Symptoms/Infection	5.7	6.8
Rash	1.9	2.9
Ear Infection/Otitis Media	1.1	2.4
Conjunctivitis	0.3	1.0

n = Number of subjects evaluated.

TABLE 3

Antibody Responses of Infants and Children to PedvaxHIB™

Age (Months)	No. of Subjects	Time	% Subjects with Anti-PRP >0.15 mcg/ml	% Subjects with Anti-PRP >1.0 mcg/ml	Post-Vaccination Anti-PRP GMT (mcg/ml)
2-3	113	Dose 1**	97	81	2.48
		Dose 2***	98	88	4.60
4-14	252	Dose 1**	98	75	2.53
		Dose 2***	100	92	6.04
15-71	170	Single Dose**	99	91	6.12

* Only subjects with prevaccination anti-PRP $\leq$ 0.15 mcg/ml are included in this table (excluding Native Americans).

** Two months after vaccination.

*** One month after vaccination.

TABLE 4

Antibody Responses of Infants to Booster
Vaccination at 12-17 Months of Age with PedvaxHIB™

Age (Mos) at Primary Vaccination	No. of Subjects	Time	% Subjects with Anti-PRP >0.15 mcg/ml	% Subjects with Anti-PRP >1.0 mcg/ml	GMT (mcg/ml)
2-3	23	Pre-booster	87	22	0.54
		Post-booster*	100	96	14.53
4-11	20	Post-booster	90	50	0.95
		Pre-booster*	100	95	21.64

* One month after revaccination