SUMMARY FOR THE BASIS OF APPROVAL

Reference Number:
95-0458 (STN 103623/0)

Drug Licensed Name:
Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine

Manufacturer:
Merck & Co., Inc.

Drug Trade Name:
COMVAX™

COMVAX™ [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine] is a sterile bivalent vaccine made of the antigenic components used in producing PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] and RECOMBIVAX HB® [Hepatitis B Vaccine (Recombinant)]. These components are the *Haemophilus influenzae* type b capsular polysaccharide [polyribosylribitol phosphate (PRP)] that is covalently bound to an outer membrane protein complex (OMPC) of *Neisseria meningitidis* and hepatitis b surface antigen (HBsAg) from recombinant yeast cultures.

I. INDICATIONS AND USAGE:

COMVAX is indicated for vaccination against invasive disease caused by *Haemophilus influenzae* type b and against infection caused by all known subtypes of hepatitis B virus in infants 6 weeks to 15 months of age born of HBsAg negative mothers.

II. DOSAGE AND ADMINISTRATION:

COMVAX™ is a sterile suspension intended for intramuscular injection, with the *anterolateral thigh* being the recommended injection site for infants. Injection must be accomplished with a needle long enough to ensure intramuscular deposition of the vaccine.

Each 0.5 ml dose of COMVAX™ is formulated to contain 7.5 mcg of PRP conjugated to approximately 125 mcg of OMPC, 5 mcg of HBsAg, approximately 225 mcg aluminum as aluminum hydroxide, and 35 mcg sodium borate (decahydrate) as a pH stabilizer, in 0.9% sodium chloride. Infants should be vaccinated with three 0.5 mL doses of COMVAX™, ideally at 2, 4, and 12-15 months of age. If the recommended schedule cannot be followed, the interval between the first two doses should be at least 6 weeks and the interval between the second and third dose should be as close as possible to 8 to 11 months.

Vaccination schedules for children not vaccinated according to the recommended schedule should be considered on an individual basis. The number of doses of a PRP-OMPC-containing product (i.e., COMVAX™, PedvaxHIB®) depends on the age that vaccination is begun. **An** infant 2 to 10 months of age should receive three doses of a product containing PRP-OMPC. An infant 11 to 14 months of age should receive two doses of a product containing PRP-OMPC. A child 15 to 71 months of age should receive one dose of a product containing PRP-OMPC. Infants and children, regardless of age, should receive three doses of an HBsAg-containing product.

Children who receive one dose of hepatitis B vaccine at or shortly after birth may be administered COMVAX™ on the schedule of 2, 4, and 12-15 months of age. There are no data to support the use of a three-dose series of COMVAX™ in infants who have previously received more than one dose of hepatitis B vaccine. **However, COMVAX™ may be** administered to children otherwise scheduled to receive concurrent RECOMBIVAX HB® and PedvaxHIB®.

Infants born to HBsAg positive mothers should receive Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see manufacturer's circular for Hepatitis B Vaccine [Recombinant]). Infants born to mothers of unknown HBsAg status should receive Hepatitis B vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see manufacturer's circular for Hepatitis B Vaccine [Recombinant]).

Results from clinical studies indicate that COMVAX™ can be administered concomitantly with DTP, OPV, and M-M-R®$_{II}$, and with a booster dose of DTaP at approximately 15 months of age, using separate sites and syringes for injectable vaccines. No impairment of immune response to these individually tested vaccine antigens was demonstrated.

At the time of approval, data were not available regarding concomitant administration with IPV, VARIVAX [Varicella virus vaccine, live (Oka/Merck)] or with the primary series of DTaP.

III. MANUFACTURING AND CONTROLS

A. Manufacturing and Controls

COMVAX™ is a bivalent vaccine that contains the active components of two licensed vaccines - liquid PedvaxHIB® and RECOMBIVAX HB®, as a pre-mixed, aluminum hydroxide adsorbed, preservative-free, liquid formulation. PedvaxHIB® is a vaccine based on the capsular polysaccharide, polyribosylribitol phosphate (PRP), from *Haemophilus*

influenzae type b linked covalently to the outer membrane protein complex (OMPC) of the B11 strain of *Neisseria meningitidis* serogroup B RECOMBIVAX HB® is a vaccine based on hepatitis B surface antigen (HBsAg) derived from a recombinant strain of *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of the viral subunit.

H. influenzae type b and *N. meningitidis* serogroup B are each grown in complex fermentation medium and then inactivated by the [redacted]. The primary ingredients of the [redacted]-inactivated fermentation medium for *Haemophilus influenzae* include an [redacted] and for *Neisseria meningitidis* include an [redacted].

The PRP from *Haemophilus influenzae* is purified from the culture broth by purification procedures that include ethanol fractionation, enzyme digestion, phenol extraction, diafiltration, [redacted]. The OMPC from *N. meningitidis* is purified by detergent extraction, centrifugation, [redacted]. The purified OMPC is sterilized by [redacted] diafiltered [redacted].

The PRP-OMPC conjugate is prepared by chemical coupling of the PRP to OMPC. The OMPC is activated by [redacted] and the PRP is reacted by a series of chemical reactions to [redacted]. Conjugation results in the formation of [redacted] which provide the covalent linkages between the PRP and OMPC. [redacted] diafiltration are used to purify the conjugate product. After conjugation, the aqueous PRP-OMPC bulk is [redacted] and adsorbed onto aluminum hydroxide.

A portion of the hepatitis B virus gene, coding for HBsAg, is cloned into yeast, and the vaccine for hepatitis B is produced from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae*. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods. The aqueous bulk is treated with formaldehyde and then formulated with an aluminum hydroxide adjuvant.

The manufacture of COMVAX™ consists of combining the PedvaxHIB® and RECOMBIVAX HB® bulks and filling the vaccine without preservatives into single dose vials. Each 0.5 mL dose contains 7.5 mcg PRP conjugated to approximately 125 mcg of OMPC, 5 mcg of HBsAg, approximately 225 mcg aluminum as aluminum hydroxide, and 35 mcg sodium borate (decahydrate) as a pH stabilizer, in 0.9% sodium chloride. The vaccine contains [redacted] (w/v) residual formaldehyde.

In-process monitoring is carried out to confirm [redacted]

[redacted] and [redacted] for each of the components. Each of the bulk components is tested for [redacted] of [redacted] by various [redacted]. The final product is extensively tested to ensure safety, potency, and appropriate biochemical and physical properties. The potency of the PRP-OMPC component is measured by quantitating the polysaccharide concentration by an [redacted] method. The potency of the HBsAg component is measured relative to a standard by an [redacted] immunoassay.

B. Stability

A combination of [redacted] assays are used to monitor the stability of the Liquid PedvaxHIB© Adsorbed Bulk and RECOMBIVAX HB® bulk alum product intermediates. Stability studies on the bulk intermediates have confirmed that the bulk products are stable for at least 12 months at 2-8° C storage conditions. Stability data on COMVAX™ Final Container vaccine shows that the product is stable for 18 months at 2-8° C storage. At an elevated storage temperature of [redacted] C for [redacted] months, no instability was observed. At [redacted] C storage for 3 months, some sporadic [redacted] instability was observed. However, the recommended storage of the product is at 2-8° C.

C. Validation

The major equipment used in the manufacture and filling of the product has been validated. Appropriate specifications have been established for monitoring environmental conditions during each critical step of manufacture of the product at the manufacturing facilities.

D. Labeling

The labeling, including the package insert, has been reviewed for compliance with 21 CFR 610.60, 610.61, 610.62, 201.56 and 201.57 and found to be satisfactory. The container label includes a warning statement indicating "Do Not Inject Intravenously, Intradermally, or Subcutaneously," a cautionary statement that federal law prohibits dispensing without a prescription, a statement to "Shake Well Before Using," a statement to store at 2-8° C (35.6 - 46.4° F), and a warning statement "Do Not Freeze."

The package insert 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.

The trade name COMVAX™ is not in conflict with the name of any other vaccine trade names.

E. Establishment Inspection

A pre-license inspection of the Merck & Co., Inc. biological production facilities used in production of COMVAX™ was conducted September 10 through September 13 and September 23, 1996. Responses to inspectional observations and corrective actions were adequate, and the facility was considered to be in compliance with GMP regulations.

F. Environmental Impact Analysis Report

An environmental impact assessment to reflect use of COMVAX™ was submitted on March 31, 1995. **A finding of no significant impact** was found. There was no indication of a necessity for further environmental impact analysis.

IV. PHARMACOLOGY

Antibody (anti-PRP) specific for the capsular polysaccharide of *Haemophilus influenzae* type b affords protection against invasive disease. **The serum level of anti-PRP induced by vaccination is** measured with a [redacted] according to a protocol and with standards mandated by the U.S. FDA. In this assay, serial [redacted] dilutions of serum are incubated with [redacted] Immunoglobulins are then [redacted] The final assigned titer for a given serum is the [redacted] As currently used, the minimum concentration of anti-PRP defined by this test is [redacted] mcg/mL.

Antibody (anti-HBs) to HBsAg protects against HBV infection. The serum level of anti-HBs can be measured with either a radioimmunoassay or an enzyme linked immunoassay. Antibody was measured with the AUSAB® **radioimmunoassay test kit produced by** [redacted] **during the** clinical development of COMVAX™. With this assay, aliquots of serum are [redacted] A sample is considered positive for anti-HBs [redacted] Anti-HBs titers in terms of mIU/mL are calculated [redacted]

Animal toxicity studies were not deemed necessary for COMVAX™ because COMVAX™ is a combination of already licensed products. A major concern for approval focused on the demonstration of equivalent immunogenicity of the combined vs. separate products. The manufacturer's labeling is adequate with respect to pharmacology of COMVAX™.

V. MEDICAL

A. General Information

Prior to the introduction of Haemophilus b conjugate vaccines, *Haemophilus influenzae* type b (Hib) has been the most frequent cause of bacterial meningitis and a leading cause of other serious bacterial diseases in young children, including cellulitis, epiglottitis, sepsis, pneumonia, septic arthritis, osteomyelitis and pericarditis. Approximately 85% of the cases of this invasive disease involved children less than 5 years of age, and nearly half of all cases occurred by 1 year of age. **Invasive Hib disease can be prevented with** vaccines comprised of the bacterial polysaccharide polyribosylribitol phosphate (PRP) chemically conjugated to a protein carrier. Routine immunization with such a Hib vaccine is recommended for all infants in the U.S.

Infection and related liver disease due to hepatitis B virus (HBV) present a significant public health problem. Illness associated with acute infection can debilitate a patient for weeks or months, and occasionally has a fatal outcome. Chronic infection can ultimately lead to the development of chronic active hepatitis, cirrhosis, or primary hepatocellular carcinoma. When infected, infants and children are much less likely than adults to experience clinical illness during acute infection, but they are at much higher risk than adults of becoming chronic carriers of the virus. In the United States and other highly developed countries with a relatively low incidence of hepatitis B, a large majority of the HBV infections occur during adolescence or adulthood. HBV infection can be prevented with vaccines comprised of purified viral surface antigen (HbsAg). Routine immunization with hepatitis B vaccine is recommended for all infants in the U.S. as a means of creating broad-based immunity in the population at an early age, before individuals enter occupations or develop behaviors that place them at increased risk of exposure to virus.

Efficacy:

An efficacy study with clinical end points was not performed with COMVAX™ (PR). However, efficacy had been demonstrated for the monovalent components, and efficacy was inferred from the studies performed with PR by demonstrating that the immune responses to HBsAg and PRP were not inferior to those obtained in the control group

receiving the monovalent components by separate but simultaneous injection.

Antibody to the polyribosylribitol phosphate polysaccharide of *Haemophilus influenzae* type b (anti-PRP) protects against invasive Hib disease. While the level of anti-PRP required for protection has never been defined precisely, studies of Hib polysaccharide immune globulin and of an unconjugated PRP vaccine have associated protection with anti-PRP titers of >0.15 mcg/mL and >1.0 mcg/mL, the lower titer being viewed as conferring immediate protection with the higher titer seen as a desirable target level to ensure long-term protection. Furthermore, the protective efficacy of the PRP-OMPC component of COMVAX™ has been demonstrated in a randomized, double-blind, placebo-controlled study involving 3486 Native American (Navajo) infants (The Protective Efficacy Study), who completed the primary two-dose regimen of lyophilized PedvaxHIB®. **Each infant in the study received two doses of** either placebo or lyophilized PedvaxHIB®, with the initial dose of vaccine given at a mean age of 8 weeks and the second dose given approximately two months later. In a subset of 416 subjects, lyophilized PedvaxHIB® induced anti-PRP levels >0.15 mcg/ml in 91% and >1.0 mcg/ml in 60% with a GMT of 1.43 mcg/ml, 1 to 3 months after the second dose. Most subjects in the Protective Efficacy Study were followed through 15 to 18 months of age. During that time, 22 cases of invasive Hib disease occurred in the placebo group versus a single case in the vaccine group. **Thus, the protective efficacy after the primary** two-dose regimen was estimated to be 93% (95% C.I. 57%, 98%).

With respect to hepatitis B, multiple randomized, double-blind, placebo-controlled efficacy trials of plasma-derived hepatitis B vaccines have shown that vaccinees who develop an anti-HBs level of at least 10 mIU/mL after vaccination have virtually complete protection against clinically significant infection. The protective efficacy of RECOMBIVAX HB® has also been demonstrated in the very high-risk infants born to carrier mothers positive for both HBsAg and HBeAg. **In a** clinical study of such infants given one dose of Hepatitis B Immune Globulin at birth followed by 5 mcg doses of RECOMBIVAX HB® at birth, 1, and 6 months of age, chronic HBV infection had not occurred in 96% of 130 infants after nine months of follow-up. **The estimated efficacy** in prevention of chronic HBV infection was 95% as compared to the infection rate in untreated historical controls.

The anti-PRP and anti-HBs responses of children to a course of vaccination with COMVAX™ indicate that the efficacy of COMVAX™ would be similar to that of PedvaxHIB® and of RECOMBIVAX HB®.

B. Clinical Studies

The monovalent *Haemophilus influenzae* type b and hepatitis B vaccines combined in COMVAX™ have had extensive use prior to the clinical development of this bivalent formula. By early 1995, more than 4.7 million doses of lyophilized PedvaxHIB® and more than 55 million doses of RECOMBIVAX HB® had been sold worldwide. PedvaxHIB® has been used exclusively in children, while most of the RECOMBIVAX HB® used to date has been administered to adults. However, since 1991 there has been increasing use of this vaccine for the immunization of infants.

Clinical studies of COMVAX™ were initiated in August of 1990. From that time until April 23, 1996, 6705 doses of COMVAX™ were administered to 2612 children in these trials. Additional studies of COMVAX™ are in progress.

Study 002:
In this open label, multicenter study, approximately 800 infants born to mothers who were seronegative for HBsAg were randomly assigned to receive 3 different lots of COMVAX™ (PR) or separate injections of P (liquid PedvaxHIB®, 7.5 μg) and R (RECOMBIVAX HB®, 5 μg). Approximately the first 50% of subjects were to be immunized at 2, 4, and 15 months of age, and the remainder at 2, 4, and 12 months of age, so that subjects would complete the study at about the same time. Originally subjects were to be allocated equally to each of the 4 treatment arms. However, because the third lot of PR was not available at the outset of the study, subjects were randomized 3:3:2 to receive the first 2 lots of PR or P + R. When the third lot became available, new subjects were randomized 3:3:6:4 to receive the first, second, or third lot of PR or P + R, respectively. Standard vaccines given concurrently with study vaccines were recorded in case report forms.

The "primary parameters of interest" for statistical comparison are the anti-PRP >1.0 μg/ml and magnitude of responses, especially after dose 2, and the proportion of subjects with anti-HBs ≥10 mIU/ml and the GMTs of these antibodies, especially after dose 3. However, serological results will be summarized for all bleeds in all groups.

Combining the 3 PR lots for a comparison of PR to P + R with respect to immunogenicity, the following power statements were provided, assuming 500 evaluable subjects in the PR arm and 165 in the P + R arm:

1. 80% power to detect a 10% point difference after 2 doses in rates of subjects having anti-PRP >1.0 μg/ml,
2. 80% power to detect an 8% point difference after 3 doses in rates of subjects having anti-HBs ≥10 mIU/ml, and
3. 80% power to detect 1.42-fold difference in anti-PRP GMTs and 1.55-fold difference in anti-HBs GMTs.

Subject characteristics: 882 infants were enrolled; 661 received PR (247 Lot 1, 237 Lot 2, and 177 Lot 3) and 221 received P + R (separate but simultaneous injection). When all 4 study arms were combined, 47% were female, 6% Asian/Pacific, 19% black, 62% white, 1% Hispanic, 7% Native American, and 5% other. Of the 882 subjects enrolled, 805 received all 3 doses of vaccine and 779 completed the study (defined by having last serology specimen obtained). Of the 103 subjects discontinued from the study, only 3 were because of AEs, namely, death due to SIDS in all 3 cases, not attributed to vaccine. See Table 1.

Table 1. Demographic Characteristics of Children Given COMVAX™ or Concurrent Injections of Liquid PedvaxHIB® and RECOMBIVAX HB® in a Large Multicenter Study

	COMVAX™	PedvaxHIB® + RECOMBIVAX HB®
Total Enrollment	661	221
Dose 1	661	221
Dose 2	645	213
Dose 3	608	197
Age at First Injection		
Median	8.0 weeks	8.0 weeks
Mean	8.3 weeks	8.2 weeks
Std. Deviation	1.3 weeks	1.3 weeks
Range	5.0-12.0 weeks	5.0-11.0 weeks
Gender		
Female	48%	45%
Male	52%	55%
Race/Ethnic Group		
Asian/Pacific	6%	7%
Black	18%	21%
Caucasian	63%	60%
Hispanic	1%	<1%
Native American	7%	7%
Other/Unknown	5%	4%
Initial Serostatus		
"-PRP >0.15 mcg/ml	33%	32%
"-HBs >2.1 S/N	14%	10%

Immunogenicity:

Anti-PRP: Primary end point

The proportion of subjects in each of the 4 vaccine arms who had anti-PRP titers >1.0 μg/ml at the primary time point for analysis (at 6 months of age, after 2 doses) was between 71% and 76%, as follows:

TABLE 2: Anti-PRP responses after 2 doses, by vaccine group

Group	% >1.0 μg/ml	95% CI	GMT (μg/ml)	95% CI
PR CW927 (n=213)	72.3	66.3, 78.3	2.7	2.2, 3.4
PR CW928 (n=210)	71.4	65.3, 77.5	2.0	1.6, 2.5
PR CW929 (n=153)	73.9	66.9, 80.8	2.8	2.1, 3.6
all 3 lots (n=576)	72.4	68.7, 76.0	2.5	2.2, 2.8
P + R (n=186)	76.3	70.2, 82.5	2.8	2.2, 3.5

There were no significant differences between the 3 PR lots with regard to the proportions of subjects with anti-PRP >1.0 mcg/ml. The equivalence of the consistency lots was evaluated by calculating the 2-sided 95% CIs on the difference in response rate (the proportion with anti-PRP >1 μg/ml). For Lot CW927 vs. Lot CW928, the CI on the difference is (-7.68, 9.90), which supports that the two lots are similar within 10 percentage points. **For the comparison of Lots CW927** + CW928 vs. Lot CW929, the CI on the difference is (-13.24, 3.08), which is not fully in the interval of (-10, 10), but there is 88% confidence that the absolute value of the true difference is less than 10 percentage points. **Reverse cumulative distribution curves (RCDC)** show that the distributions of titers for the three lots are similar; the only deviation occurs in Lot CW928 at a point that is beyond the level considered to provide long-term protection.

The 3 PR lots were then combined and compared to P + R. The proportion with anti-PRP >1.0 μg/ml after 2 doses was not significantly different in this comparison. The only significant result was a difference among the centers. There was no significant treatment-by-center interaction. For the comparison of the combined PR lots vs. P + R, the 2-sided 95% CI on the difference in response rate is (-11.23, 3.14). This estimate is not fully in the interval of (-10, 10), but there is 95% confidence that the pooled PR groups are ≤10 percentage points lower than the control group. The reverse cumulative distribution curves show "some

separation in the distributions of titers for the PR pooled lots and the P + R group at the lower titers." However, the proportions with greater than 1 μg/ml post dose 2 exceed the proportion of 60% previously associated with protective efficacy of 93% among Native American infants, and infants given 2 doses of PedvaxHIB® retain robust immunologic memory as the level of anti-PRP declines.

Anti-HBs: Primary end point

The proportion of subjects in each of the 4 vaccine arms who had anti-HBs titers ≥10 mIU/ml at the primary time point for analysis (at 13 or 16 months of age, after 3 doses) was between 97% and 100%, as follows:

Table 3: Anti-HBs responses after 3 doses, by vaccine group and schedule

Group	Age, mo. (no.)	% ≥10 mIU/ml	95% CI	GMT (mIU/ml)	95% CI
PR CW927	13 (80)	98.8	93.2, 100.0	5094	3268, 7941
	16 (136)	99.3	96.0, 100.0	4909	3496, 6894
PR CW928	13 (70)	97.1	90.0, 99.7	4073	2550, 6504
	16 (128)	97.7	93.3, 99.6	5090	3575, 7247
PR CW929	13 (156)	98.7	95.4, 99.9	3583	2588, 4960
	16 (1)	100		10886	
all 3 lots	13 (306)	98.4	96.2, 99.6	4045	3223, 5076
	16 (265)	98.5	96.1, 99.6	5011	3932, 6385
	13 + 16	98.4	97.0, 99.3	4468*	3786, 5271
P + R	13 (96)	100.0	96.2, 100.0	6597	4963, 8767
	16 (83)	100.0	95.6, 100.0	7368	5157,10527
	13 + 16	100.0	97.9, 100.0	6944*	5556, 8679

*4468 vs. 6944, p=0.011

There were no significant differences in the proportion who had ≥10 mIU/ml after 3 doses between the PR lots. All of the CIs for the between-lot differences are well within the interval (-10, 10). The CI for the difference between the combined PR lots vs. P + R is (-2.93, -0.56). **These data support the conclusion of equivalence among the** three lots of PR and between the combined PR lots and P + R with regard to the percentage attaining anti-HBs ≥10 mIU/ml.

Anti-HBs GMTs were compared post-dose 3 between PR lots. No significant differences were noted. The comparison of post-dose 3 GMTs for the combined PR groups vs. P + R showed a significant difference

among centers ($p<0.001$) and between PR and P + R (4468 vs. 6944 mIU/ml, $p=0.011$). **Although the difference between PR and P + R is** statistically significant, both values are much greater than the level of 10 mIU/ml previously established as marking a protective response to hepatitis B. **These GMTs are also higher than those** reported in a number of studies wherein healthy neonates or young infants received the currently licensed regimen of RECOMBIVAX HB® consisting of 2.5 μg doses administered on the standard 0, 1, and 6 month schedule. In those studies the infants developed GMTs of 216-1269 mIU/ml. **Another study has shown that infants given 2.5 μg** doses of Recombivax HB according to the schedule used for COMVAX™ (2, 4, and 12 or 15 months of age) developed GMTs of 1356 - 3424 mIU/ml.

Antibody Responses to Polio Vaccine:
Antibody responses to polio types 1, 2, and 3 were measured in 39 COMVAX™ recipients at 7 months of age, after 3 doses of DTP at 2, 4, and 6 months of age and 2 doses of OPV at 2 and 4 months of age. The vaccines at 2 and 4 months of age were given concurrently with COMVAX™. **The proportion with detectable neutralizing antibody to** polio was 90% for type 1, 100% for type 2, and 92% for type 3 (N = 39).

Antibody Responses to MMR Vaccine:
COMVAX™ recipients (N = 63) and P + R recipients (N = 51) were tested for antibody to MMR after receiving MMR vaccine concurrent with COMVAX™ or P + R at 12-15 months of age. The primary end point was defined as the proportion of seronegative subjects who became seropositive after vaccination with MMR. **The response rates ranged** from 93 to 100% for the three antigens.

Safety (Study 002):
The incidence of reported AEs from this pivotal study are summarized in Table 2 of the package insert (See attached package insert).

Parents were asked to record temperature (Vaccination Report Card indicates that temperature can be taken by rectal or axillary routes), injection-site reactions, and systemic complaints on days 0-5 after each immunization on "Vaccination Report Card" and to notify study physician if unexpected or serious reactions occurred; subjects with clinically significant experience were seen by an RN or physician; serious AEs that occurred within 14 days of vaccination were recorded in detail in case report forms; all serious events that occurred any time on study or within 14 days of completion of study were to be reported to the clinical monitor.

Across all 4 treatment groups, 89% (787/881) of the subjects with clinical follow-up reported systemic or injection site reactions

within 5 days of any injection. The overall frequency of AEs was 90% (593/660) in the combined PR groups and 88% (194/221) in the P + R group. **Serious AEs, none of which were attributable to** vaccine, occurred in 17 subjects within 14 days of any injection (5 received PR Lot 1, 1 received PR Lot 2, 6 received PR Lot 3, and 5 received P + R). Three subjects died of SIDS during the study: Case **no [redacted] in the P + R group died 29 days after dose 1; Case [redacted] in** the P + R group died 31 days after dose 2; Case no. [redacted] in the PR Lot CW928 group died 38 days after dose 1; none of these deaths was reported as related to the vaccine. Statistical comparisons were made between the three PR lots and between PR and P + R for subjects with AEs (injection site and systemic), with vaccine-related AEs, with serious AEs, deaths, or discontinuation because of AEs; no differences were found.

The three PR groups were pooled and compared with the P + R group after each dose (See Table 2 of attached package insert). When the combined PR groups are compared to the P + R group over all injections, any injection site AE occurred in 70% (463/660) of the PR recipients and 72% (159/221) of the P + R recipients (69% to P, 52% to R). Any systemic AE occurred in 84% and 80% of each group, respectively. **Irritability occurred more frequently in the PR group** than in the P + R group (75% vs. 67%, p=0.045). Fever (5.3% vs. 5.9%), prolonged crying (3.3% vs. 3.6%), unusual, high-pitched crying (16% vs. 12%), and somnolence (64% vs. 58%) occurred at comparable rates in the two groups.

The safety profile of the study vaccine was evaluated in the context of concurrent immunization with routine childhood vaccines, i.e., 82-85% of subjects received OPV and DTP (or DT) concurrent with doses 1 and 2 of PR or P + R, and 31% received MMR concurrent with dose 3 (16-32% of each of the three PR groups and 27% of the P + R group).

Study 004:

In this open, multicenter study, 126 healthy infants who had received a dose of hepatitis B vaccine at birth and who were born to HBsAg negative mothers were randomly assigned to one of two treatment groups. All subjects received PR at 2, 4, and 15 months of age and both groups received the same concurrently administered vaccines at 4, 6, and 15 months of age. The groups differed only in that at 2 months of age, either an investigational DTP/IPV vaccine or licensed DTP and OPV vaccines were administered.

Subject characteristics

126 subjects were enrolled at 3 centers in the U.S., with 62 receiving the investigational DTP/IPV combination vaccine and 64 receiving DTP and OPV at 2 months of age. **The group as a whole** was

43% female, had a mean age of 8.9 weeks at outset, and was 65% black and 33% white.

Of the 126 subjects enrolled, 118 received the immunizations scheduled at 2, 4, and 6 months of age, and 117 were continuing in the study at the time of the primary clinical review. Subsequently, 94 subjects received the third dose of COMVAX™ at 14-15 months of age and completed the study. One subject discontinued because of AEs. This subject, who had a history of seizures under control at study entry, was diagnosed with CNS anomaly, diabetes insipidus, and seizure disorders 7 months after the vaccinations at 6 months of age; none of these serious AEs was attributed to vaccine.

Immunogenicity

Anti-PRP

The primary end point was the proportion of subjects with anti-PRP titer >1.0 μg/ml at 6 months of age (after 2 doses of PR vaccine). Of 111 subjects, 81% (90% CI 74,87) had anti-PRP titers >1.0 μg/ml at 6 months of age.

The secondary end points were the proportion with anti-PRP >0.15 μg/ml (95%) and the GMT (3.3 μg/ml) at 6 months of age.

Anti-HBs

The primary end point was the proportion of subjects with anti-HBs titers ≥10 mIU/ml at 6 months of age, after 3 doses of hepatitis B vaccine (study infants had been vaccinated with hepatitis B vaccine at birth and then received PR vaccine at 2 and 4 months of age). Of 111 subjects, 98% (90% CI 94,100) had this level of anti-HBs titers. The secondary end points at 6 months of age included the proportion with anti-HBs ≥2.1 S/N (99%) and the GMT (417 mIU/ml).

Antibody Responses to Polio Vaccine:

In the group receiving licensed oral polio vaccine concurrent with PR at 2 and 4 months of age (i.e., after two or three doses), the percent with detectable neutralizing antibody to polio was 80% for polio type 1 (N = 54), 95% for type 2 (N = 55), and 85% for type 3 (N = 54). A subgroup (N = 16) of those who received a third dose of OPV at 15 months of age was tested for polio antibody; 100% had detectable neutralizing to polio types 1, 2, and 3.

Antibody Responses to D and T Toxoids:

The percentage of subjects with a four-fold antibody rise after 3 doses of DTP was 99% for tetanus (N = 105, [redacted] assay) and 90% for diphtheria (N = 107, [redacted] assay). This response was similar to historical data for Connaught DTP. At 7 months of age, 97.2% (104/107) of subjects had diphtheria titers ≥0.02 units/ml, and 100%

(106/106) had tetanus titers ≥0.02 equivalents/ml. [redacted] Inc. tested a number of sera evaluated in the [redacted] assays which had lower titers for antibody to diphtheria in an *in vivo* rabbit protection study and a number of sera evaluated in the [redacted] assays which had lower titers to tetanus in an *in vivo* mouse assay. Their results showed that subjects with Vero cell anti-diphtheria titers and tetanus [redacted] titers as low as 0.02 units/ml and 0.02 equivalents/ml respectively would have protective antibodies of ≥0.01 IU/ml in the *in vivo* assays.

Antibody Responses to Pertussis Antigens:
The percentage of subjects with a four-fold antibody rise after 3 doses of DTP was 89% for pertussis agglutinogens (N = 101), 86% for FHA (N = 103), 90% for PT (N = 104), and 70% for the [redacted] assay for anti-pertussis toxin (N = 103). These responses were similar to historical data for Connaught DTP.

Study 004 Safety:
The safety monitoring for Study 004 was similar to that used in Study 002, and the adverse event profile was generally similar to that observed in Study 002. However, the incidence of prolonged crying was greater in Study 004. There was a similar frequency of prolonged crying in the COMVAX™ and P + R groups in Protocol 002 and in the COMVAX™, P + R, and P followed one month later by R groups in Protocol 005 (see below). When the data for the first two doses of PR were combined, there were 21 episodes of prolonged crying out of 1305 doses (1.6%) in Protocol 002, 26/250 (10.4%) in Protocol 004, and 6/137 (4.4%) in Protocol 005 (see below), with an overall rate in the three protocols combined of 53/1692 doses (3.1%). In a protocol [redacted] conducted by [redacted] Inc., COMVAX™ was administered concurrently with DTP/IPV at 2 and 4 months of age to 527 subjects for a total of 1045 doses. Only one subject reported prolonged crying (>3 hours) in the 72 hours post-vaccination, for a rate of 1/1045 doses (0.1%). The sponsor suggests "that this AE is less likely to be attributable to DTP/IPV or PR and perhaps having more to do with method of data collection," and this observation may be the result of differences between studies in event ascertainment.

In study 004, serious AEs, of which none was attributable to vaccine, occurred in 8 subjects during the study. (The sponsor reported 3 additional subjects with "serious AEs"; these subjects received a double dose of DTPa vaccine at the 14-15 month visit, but their AEs were mild to moderate and transient.) The only serious AE within 14 days of any injection occurred 12 days after immunization with DTP/IPV and PR at 2 months of age. This AE was diagnosed as a viral infection with upper respiratory symptoms, and the infant recovered after a 3-day hospitalization. No deaths were reported.

Study 005:
In this open-label, multicenter study, 208 infants were randomized to receive at 2, 4, and 15 months of age 1) PR combination vaccine; 2) P+R as separate, but concurrently administered injections; or 3) P, followed by R one month later. **The demographic distribution was** 87% Caucasian, 8% African-American, 2% Hispanic, 2% Asian/Pacific, and 2% other. **All subjects received concurrently administered,** licensed vaccines as follows: DTP (Connaught Laboratories Inc) and OPV (Lederle) at 2, 4, and 6 months of age, MMR at 15 months of age, and DTaP at 16 months of age. **Sixty-four of 69 subjects in the PR** group, 54/69 in the P+R group, and 49/70 in the P followed by R group completed the vaccination schedule through 16 months of age. One study subject (Case number 00279, P followed by R group) discontinued the study because of an adverse experience, which was characterized by petechia from a blood draw. **One subject (Case** number 00214) in the P + R treatment group, who was evaluated for possible developmental delay at 15 months of age, was advised not to receive further DTP vaccination and was dropped from the study.

Immunogenicity
Anti-PRP
The percentage of subjects in each of the three vaccine arms who had anti-PRP >1 μg/ml at the primary time point (6 months of age, after two doses of vaccine) was 79% in the PR group, 84% in the P+R group, and 76% in the P followed by R group.

Table 4: Anti-PRP responses after 2 or 3 doses of PR, P+R, or P followed by R

Group (n)	% >0.15 μg/ml	% >1 μg/ml (95% CI)	GMT (μg/ml)
PR			
PD* 2 (62)	98	79 (67, 88)	2.94
PD 3 (56)	100	95 (85, 99)	7.54
P+R			
PD 2 (61)	95	84 (72, 92)	3.15
PD 3 (47)	98	89 (77, 97)	7.72
P, then R			
PD 2 (45)	98	76 (61, 87)	3.77
PD 3 (47)	98	92 (80, 98)	11.28

*PD = post-dose

Anti-HBs

The percentage of subjects in each of the three vaccine arms who had anti-HBs ≥10 mIU/ml at the primary time point (6 months of age, after two doses of study vaccine) was 97% in the PR group, 93% in the P+R group, and 98% in the P followed by R group. **The P followed** by R group differs from the other two groups in that the anti-HBs responses were measured 1 month after vaccination vs. 2 months after vaccination for the other two groups. Also, a greater proportion of subjects in the P followed by R group had received a hepatitis B vaccine prior to study entry: 27/70 (38.6%) vs. 19/69 (27.5%) in the PR group and 21/69 (30.4%) in the P+R group. These differences would be expected to increase the anti-HBs response in the P followed by R group.

Table 5: Anti-HBs responses after 2 or 3 doses of PR, P+R, or P followed by R

Group (n)	% >10 mIU/ml (95% CI)	GMT (mIU/ml) (95% CI)
PR		
PD* 2 (59)	97 (88, 100)	213 (135, 335)
PD 3 (57)	100 (94, 100)	2066 (1299, 3286)
P+R		
PD 2 (60)	93 (84, 98)	201 (124, 324)
PD 3 (47)	100 (93, 100)	2305 (1488, 3571)
P, then R		
PD 2 (50)	98 (89, 100)	340 (220, 526)
PD 3 (48)	100 (93, 100)	2230 (1525, 3261)

*PD = post-dose

The reverse cumulative distribution curves for the three groups were similar. **Although there are some separations at higher titers,** these were not felt to be clinically relevant because most of them occurred above the level of >1 μg/ml for anti-PRP and ≥10 mIU/ml for anti-HBs.

Antibody responses to polio vaccine

The primary endpoint was the proportion in each study group with detectable neutralizing antibody to poliovirus types 1, 2, and 3 at 7 months of age, after receiving a 3-dose regimen of OPV at 2, 4, and 6 months of age. After the third dose of OPV, 98-100% of the subjects had detectable antibody to each poliovirus type in each treatment group (N = 50-57), and the lower bound of the 95% CI was at least 90% in all cases. **This compares favorably with the** expected response rate of 90%. The reverse cumulative distribution curves for antibodies to types 1, 2, or 3 for the three treatment

groups are also similar.

Antibody responses to DTP vaccine

The primary endpoint was the proportion of subjects with a ≥4-fold rise in antibody at 7 months of age, after three doses of DTP, relative to the baseline value at 2 months of age, adjusted for the decay of maternal antibody. **The percentage of subjects in each** treatment group with such antibody rises was 94-98% for diphtheria (N = 52-57), 100% for tetanus (N = 52-57), 95-100% for pertussis agglutinins (N = 52-57), 90-98% for anti-FHA (N = 52-57), 95-98% for anti-LPF (N = 52-57), and 93% for [redacted] assay (N = 52-57). These responses compared favorably with the expected response rate of 90% and with historical controls. The three treatment groups also appeared similar in their response to a booster dose of DTaP at 16 months of age. The reverse cumulative distribution curves showed that nearly all infants had diphtheria and tetanus titers above 0.02 units/ml and 0.02 equivalents/ml, respectively, after three doses of DTP. **Sera with such values are likely to have protective** levels of antibody based on an in vivo neutralizing assay of such serum samples.

Antibody responses to MMR vaccine

The primary endpoint was the proportion of subjects in each treatment group seropositive for measles, mumps, and rubella antibody at 17 months of age, 2 months after vaccination with MMR. Because pre-MMR vaccination serum specimens at 15 months of age were not available for most subjects, the data are summarized without regard to initial serostatus. **All subjects were seropositive for** mumps (N = 48-56) and rubella (N = 48-57) antibody, with the lower bound of the 95% CI equal to or greater than 92% for all 3 treatment groups. **Measles antibody seropositivity was 93% for the PR group** (N = 56), and 96% each for the P+R (N = 47), and P followed by R groups (N = 48); the lower bound of the 95% CI was 83% for the PR group and 86% for the other two groups. **These results compare** favorably with the expected response of 95%.

Safety:

Injection site AEs within 14 days after vaccination for the PR group were not markedly different from the P+R group or the monovalent P vaccination of the P followed by R group. **Systemic AEs occurred** with similar frequency in the PR and P+R groups. Three serious AEs were reported, none of which were attributable to vaccine. Only one of these AEs occurred within 14 days post-vaccination: a subject in the P+R group was hospitalized for wheezing, which began 4 days after receiving DTP and OPV at 6 months of age.

Additional Studies:
In Studies [redacted] and -02, 821 infants received 2410 doses of PR at 2, 4, and 15 months of age, concurrently with investigational DTP/IPV at 2 and 4 months and with other routine vaccines (MMR, OPV, DTaP) at 15 months of age. In Studies 013 and 014, 935 infants received 1832 doses of PR, mostly at 2 and 4 months of age, concurrently with investigational pneumococcal conjugate vaccine and licensed DTP and OPV vaccines. In these studies combined, a total of 1756 infants received 4242 doses of PR.

Serious Adverse Experiences:
The serious AEs that occurred within 14 days after vaccination with PR in these studies are noted below. None was attributed to vaccination with PR.

In Protocol [redacted] (294 subjects who received 855 doses of PR), one subject had a viral URI 6 **days after** receiving DTP/IPV and PR at 2 months of age. In Protocol [redacted] (527 subjects who received 1555 doses of PR), no serious AEs within 14 days after PR vaccination were reported.

In Protocol 013 (721 subjects who received 1392 doses of PR), six subjects had serious AEs within 14 days after vaccination with PR, DTP, OPV, and pneumococcal conjugate vaccine or placebo. These AEs included RSV, respiratory distress, bronchiolitis, viral gastroenteritis, and skull fracture.

One death was reported during the study. This infant died of SIDS 26 days after receiving his second injection of PR, DTP, OPV, and placebo.

In protocol 014 (214 subjects who received 435 doses of PR), two subjects had serious AEs within 14 days after vaccination with PR, DTP, OPV, and pneumococcal conjugate vaccine. The AEs included bronchiolitis, pneumonia, and RSV.

Overall Safety Database:
The overall safety database for serious AEs includes 2612 infants who have received a total of 6705 doses of PR at 2, 4, and 12-15 months of age. No serious AEs were attributed to vaccination with PR. The database for all injection site and systemic AEs, including temperature elevations, includes 856 infants who have received a total of 2404 doses of PR. **The frequency of unusual, high-pitched** crying and prolonged crying was higher than expected, but occurred with similar frequency in the P + R control arm and was not associated with any serious AEs. **Of note, no study subject was** discontinued due to vaccine-related AEs.

Because of the large safety database available for PedvaxHIB® and RECOMBIVAX HB®, the basic components of the PR combination vaccine, PR is approvable on the basis of the database of 2612 infants.

A commitment from Merck was obtained to perform a Phase 4 study to obtain safety data in an additional 5,000 infants 2 to 15 months of age, who will receive three doses of COMVAX™. **Merck also committed** to submit for CBER review the results of on-going studies to evaluate immunogenicity of Varicella Vaccine, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine (primary immunization), and Polio Virus Vaccine Inactivated when administered concurrently with COMVAX™; the package insert for COMVAX™ will be revised to include the results of the studies on concurrent immunization of COMVAX™ with these pediatric vaccines.

VI. Advisory Committee consideration.

PedvaxHIB® and Recombivax HB® are licensed products whose safety and efficacy are well established. No new safety or efficacy issues were raised in the review of COMVAX™, and it was determined that it was not necessary to bring COMVAX™ before the Vaccines and Related Biological Products Advisory Committee.

Liquid PedvaxHIB® was presented at the July 11, 1996, advisory committee meeting.

VII. Approved package insert

The approved package insert is attached. The labeling is appropriate and adequate for the product.

Stephen Feinstone, M.D.
Chairman

Karen Midthun, M.D.

Donna Chandler, Ph.D.

Carl Frasch, Ph.D.

(Getson, Weir, Daemer, Bash)