Summary for Basis of Approval

Reference Number:
95-1270
95-1267

Drug Licensed Name:
Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed (DTaP)

Manufacturer:
Pasteur Merieux Serums & Vaccins, S.A.
Connaught Laboratories, Inc

Drug Trade Name:
ActHIB ™
Tripedia™

Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), ActHIB™, is composed of the purified capsular polysaccharide isolated from *Haemophilus influenzae* type b covalently attached to tetanus toxoid prepared from the inactivated toxin of *Clostridium tetani*. ActHIB™ is lyophilized, to be reconstituted with either saline diluent, Connaught Laboratories, Inc.(CLI) DTP or Tripedia™. The vaccine, Tripedia ™ is Diphtheria and Tetanus Toxoids and Acelluar Pertussis Vaccine, adsorbed, and is a sterile solution of detoxified diphtheria and tetanus toxoids obtained from *Corynebacteria diphtheriae* and *C. tetani* respectively, and acellular pertussis vaccine in an isotonic sodium chloride solution containing sodium phosphate to control pH. The acellular pertussis component contains two *Bortetella pertussis* antigens, filamentous hemagglutinin (FHA) and inactivated pertussis toxin (PT), also known as lymphocytosis promoting factor (LPF).

I. INDICATIONS AND USAGE

ActHIB™ or ActHIB™ combined with CLI DTP vaccine by reconstitution is indicated for the active immunization of infants and children 2 through 18 months of age for the prevention of invasive disease caused by *H. influenzae* type b and/or diphtheria, tetanus and pertussis.

ActHIB™ combined with Tripedia ™ by reconstitution is indicated for the active immunization of children 15 to 18 months of age for the prevention of invasive disease caused by *H. influenzae* type b and/or diphtheria, tetanus and pertussis.

Antibody levels associated with protection may not be achieved earlier than two weeks following the last recommended dose.

Only CLI whole-cell DTP or Tripedia™ may be used for reconstitution of lyophilized ActHIB™. ActHIB™ combined with Tripedia™ by reconstitution should not be administered to infants younger than 15 months of age.

As with any vaccine, vaccination with ActHIB™ reconstituted with CLI DTP or Tripedia™ or saline diluent (0.4% sodium chloride) may not protect 100% of susceptible individuals.

II. DOSAGE AND ADMINISTRATION

When lyophilized ActHIB™ is reconstituted with Tripedia™, 0.6 ml of Tripedia™ after thorough mixing is injected into the ActHIB™ vial. After thorough mixing 0.5 ml of the mixture is withdrawn and administered intramuscularly immediately (within 30 minutes) to children 15 to 18 months of age. Each 0.5 ml dose is formulated to contain 10 µg of purified *H. influenzae* capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid, 6.7 Lf units of diphtheria toxoid, 5 Lf units of tetanus toxoid and approximately 23.4 µg each of inactivated PT and FHA protein.

III. MANUFACTURING AND CONTROLS

See the Summary for Basis of Approval dated March, 1993 for the manufacture and control of the Haemophilus b Conjugate Vaccine (tetanus toxoid conjugate), the Connaught Laboratories DTP package insert for information concerning the manufacture of DTP vaccine, and the Summary for Basis of Approval dated July 30, 1996 for the manufacture and control of Tripedia.™ The present document deals with reconstitution of ActHIB™ with Tripedia™.

A. Labeling: The package insert is in compliance with the appropriate sections, 610.60, 610.61, 610.62, 201.56, and 201.57, of 21 CFR and contains statements concerning use, contraindications, warnings, immunogenicity, experience, precautions, adverse reactions, dosage and administration, how supplied, and information on storage of the vaccine.

The package and vial labels include statements concerning the vaccine description, the proper name, the trade name, NDC number, Government license number, caution statement, storage statement, reference to directions in the circular, preservative statement, lot number and expiration date.

The trade names ActHiB™ and Tripedia™ are not in conflict with any other vaccine trade name. The labeling of Tripedia™ reflects both manufacturer of the pertussis concentrate by BIKEN and manufacture of the final product by Connaught Laboratories, Inc. The labeling of ActHiB™ reflects manufacture of the product by Pasteur Merieux Serums & Vaccins. S.A. and final packaging with Tripedia™ by Connaught Laboratories, Inc.

B. Environmental Impact Analysis: An environmental impact assessment to reflect use of DTP to reconstitute ActHIB™ was submitted on February 10, 1993. A finding of no significant impact was found. An environmental impact assessment to reflect use of Tripedia to reconstitute ActHIB™ was submitted, and a finding of no significant impact was found.

IV. PHARMACOLOGY:

The manufacturer's labeling is adequate with respect to pharmacology of both ActHIB™ and Connaught Laboratories DTaP, Tripedia™.

V. MEDICAL

A. General information:

For many years *H. influenzae* type b (Haemophilus b) has been the leading cause of invasive bacterial diseases, such as meningitis, septicemia and epiglottitis, in young children in the United States. Ninety-five percent of invasive Haemophilus b disease among children <5 years of age is caused by organisms with the type b polysaccharide capsule. Before effective vaccines were introduced, it was estimated that 1/200 children developed invasive Haemophilus b disease by 5 years of age. Sixty percent of these children had meningitis, with a 3% to 6% mortality rate. Permanent sequelae, ranging from mild hearing loss to mental retardation, affects 20% to 30% of survivors of Haemophilus b meningitis. Approximately two-thirds of all cases of invasive Haemophilus b disease occur in infants and children <15 months of age, a group for which a vaccine was not available until 1990.

It has been shown by a number of investigators that the *H. influenzae* type b capsule is a major virulence factor. Antibodies to the capsular polysaccharide are bactericidal and opsonize the bacteria for phagocytic killing. Studies in the United States showed that the peak incidence of Haemophilus b disease occurs in children between 6 and 12 months of age, a time period in which the lowest antibody levels to the organism are found. In a field trial performed in Finland in 1974, the presence of antibodies induced by an Haemophilus b polysaccharide vaccine was shown to correlate with protection. Thus protection against Haemophilus b disease is correlated with the presence of antibody to the Haemophilus b polysaccharide.

An anti-PRP antibody titer $\geq$1.0 µg/ml following vaccination with unconjugated PRP vaccine was associated with long-term protection against invasive Haemophilus b disease. Although the relevance of this antibody threshold to clinical protection after immunization with a conjugate vaccine is not known, this level continues to be considered as indicative of long-term protection.

The incidence of invasive Haemophilus b disease is higher in Native Americans, Eskimos, children of lower socioeconomic status and those with asplenia, sickle cell disease, Hodgkin's disease, or immunodeficiency syndromes. Studies also have suggested that the risk of acquiring primary invasive Haemophilus b disease under 5 years of age appears to be higher for children attending day-care facilities.

The potential for person-to-person transmission of the Haemophilus b organism among susceptible individuals has been recognized. Studies of secondary spread of disease

in household contacts of index patients have shown a substantially increased risk among exposed household members under 4 years of age.

The characteristics of an immune response depend on the type of cells producing the response and the antigens stimulating the response. Proteins induce B lymphocytes to produce antibody aided by thymus derived lymphocytes called T helper (TH) cells. Such antigens are called thymus-dependent or TD antigens. These antigens induce long lasting responses in young infants that prime for a booster type response on reexposure to the antigen. In contrast, polysaccharides stimulate B cells without TH cell help, producing a response of both IgG and IgM antibodies that does not prime for a booster type response. These antigens are called thymus-independent or TI antigens. TI antigens are poorly immunogenic at best in young infants. Chemical linkage of the Haemophilus b polysaccharide or smaller oligosaccharides to a protein carrier such as tetanus toxoid apparently converts the TI saccharide to a TD antigen. This results in an enhanced antibody response, especially in infants, to the polysaccharide that is long-lasting, and is predominantly of the IgG isotype. The conjugate importantly primes for an anamnestic response on reexposure to the polysaccharide.

Simultaneous immunization against diphtheria, tetanus, and pertussis during infancy and childhood has been a routine practice in the United States since the late 1940's. These immunizations have played a major role in markedly reducing the incidence of these diseases.

Diphtheria is primarily a localized and generalized intoxication caused by diphtheria toxin, an extracelluar protein metabolite of toxigenic strains of *C. diphtheria*. While the incidence of diphtheria in the U.S. has decreased from over 200,000 cases per year reported before 1921, before the general use of diphtheria toxoid, to only about 15 cases per year in recent years, the case fatality rate has remained at 5% to 10%, and recent localized outbreaks have occurred. Following adequate immunization with diphtheria toxoid, it is thought that protection lasts for at least 10 years. Antitoxin levels of at least 0.01 antitoxin units/ml are generally regarded as protective. This significantly reduced both the risk of developing diphtheria and the severity of clinical illness. It does not however, eliminate carriage of *C. diphtheria* in the pharynx or on the skin.

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by the potent exotoxin elaborated by *C. tetani*. The incidence of tetanus has dropped dramatically from 560 reported cases in 1947 to less than 50 cases per year in the U.S. Spores of *C. tetani* are ubiquitous, and there is essentially no natural immunity to tetanus toxin. Thus, universal infant immunization with tetanus toxoid followed by maintenance of adequate antitoxin levels, by means of timed boosters, is necessary to protect all age groups. Tetanus toxoid is a highly effective antigen and a completed primary 4 dose immunization series generally induces serum antitoxin levels of at least 0.01 antitoxin units, a level which has been associated with protective immunity.

Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis*. This gram negative bacterium produces a variety of toxins including a pyrogenic endotoxin, and a number of biologically active proteins that have been defined primarily on the basis of their activity in animals. These biologically active proteins have been associated with a number of effects including lymphocytosis, leukocytosis, sensitivity to histamine, changes in serum glucose and/or insulin levels, and possible neurological effects. The roles of each of the different components in either the pathogenesis of, or immunity to, pertussis is not understood. However, the pertussis component of the DTP vaccine clearly induces immunity against pertussis in humans.

Pertussis is a highly communicable disease that has an attack rate in unimmunized household contacts of over 90%. Since immunization against pertussis became widespread in the U.S. in the early 1950's the number of cases has declined from about 120,000 per year with a case fatality rate of about 1% to an average of 3,500 cases per year. Most reported illness from B. pertussis occurs in infants and young children, with two-thirds of reported deaths in children less than one year old.

B. Brief description of clinical studies:

The present application is for the combination of two licensed products, ActHIB™ and CLI DTaP, Tripedia™ for use as a booster dose at 15 to 18 months of age in children who have received their primary immunization series. For background information on the basis for the initial approval of ActHIB™ in March, 1993 see the Summary Basis of Approval dated March 29, 1993. For background information on the basis for the approval of ActHIB™ reconstituted with CLI whole-cell DTP see the Summary Basis of Approval dated October 28, 1993.

The present application will show that the safety profile of the ActHIB™\Tripedia™ combination is not different from the two products administered separately, and will show that there is no interference in the antibody response to any of the vaccine components.

Clinical studies for safety: Adverse reactions associated with the combination of ActHIB™ and CLI DTaP were compared to the two vaccines administered separately. The pooled safety evaluations from clinical trials in toddlers with ActHIB™ combined with Tripedia™ is summarized in Table 1. There were a total of 1113 toddlers evaluated. In addition there were 1042 infants who received the vaccine combination at 2, 4 and 6 months of age who were considered in support of the overall safety of the combination vaccine. Considering only the toddler studies the 1113 children were between 15 and 20 months of age excepting one child at 27 mo. of age (mean age 15.8 mo.). The children were closely followed for 72 hours for local and systemic reactions and 30 days post-immunization for serious and unexpected adverse events.

Table 1.

Studies for safety	Number receiving vaccine		Age group
	Separate	Combined	
U93-3109-01 (pt 1)	109	110	Toddler
U93-3109-01 (pt 2)	None	148	Toddler
468-03	None	856	Toddler
468-01, -02	Not applicable	1042	Infant

Table 7 in the attached ActHIB™ package insert provides the safety data for study U93-3109-01. No serious adverse events were seen in either the group who received the two vaccines separately or combined by reconstitution and administered within 30 minutes. There were no clinically relevant differences in local and systemic adverse reactions between the vaccines given separately or combined.

Safety data for the first 72 hours for the larger toddler safety study, 468-03, (n =856) are shown in Tables 2 and 3. Study 468-03 was an open label non-randomized safety study of the ActHIb™/Tripedia™ combination given as a booster dose to children 15 to 27 mo. of age. The mean age in this study was 16.0 mo. and 5 children were > 19.9 mo. (4 at 20 mo., 1 at 27 mo.). The study was conducted at 10 study sites. The ethnic mix was primarily Caucasian (85.6%) and African American (11.2%). There were no clinically relevant differences in the reported rates of local and systemic reactions for the comparative study (Table 7 of package insert) and those shown in Tables 2 and 3 (Note: a reaction lasting 12 hr will be counted in two columns). No hypotonic/ hyporesponsive episodes were reported. Two cases of persistent cry (0.2%) and seven with unusual cry (0.8%) were reported. Two children had seizures, one hospitalized with grand mal seizure 9 days post immunization and one possible febrile seizure 17 days post immunization. Both events were considered unrelated to vaccination.

Clinical studies for immunogenicity: Comparisons of the antibody responses to the individual vaccine components were made from the U93-3109-01 part 1 and U93-3109-01 part 2 studies. All children must have previously received three doses of DTP and Hib conjugate as infants. In all of these studies, the immune responses were essentially identical for the combined versus separate injections, except for the response to FHA (see Tables 4 and 5). Part 1 of the study was a randomized trial in children between 15 and 20 months of age (mean age 15.3), while part 2 was a randomized comparison of two additional lots of ActHIB™/Tripedia™. In both studies essentially 100% of the children boosted to ≥ 1 ug/ml of anti-Haemophilus b polysaccharide antibody.

In part 1 the geometric mean post-dose immune response to FHA was 39.81 units/ml and 44.68 units/ml for separate and combined vaccination respectively, not statistically different. However, the percent with 4-fold increase in antibody was 80.6% and 68.5%

respectively for separate and combined, statistically different at <0.05. However, use of 4-fold rise is a very artificial measure, since the important measure is not fold-rise, but whether they achieve a response associated with protection. For pertussis, levels of antibody to any one antigen associated with protection have not yet been determined. In part II of the study two lots of Tripedia™ combined with ActHIB™ induced equivalent antibody levels and fold-increases to FHA. Furthermore, when the antibody response data are plotted as a reverse cumulative distribution (see two figures), there was no difference between the percent responders to FHA at all except the highest antibody levels. Furthermore, fluctuations in the response to FHA are seen even when the DTaP vaccine, Tripedia™, is not given in combination with ActHIB™. Children receiving the DTaP/ActHIB™ combination for booster have previously received three doses of a product containing pertussis, and they will receive an additional pertussis-containing product at 4-6 years (their fifth dose). All evidence would strongly suggest that these children receiving the DTaP/ActHIB™ combination are protected against pertussis.

The FDA learned that at the time the ELISA determinations for this study for anti-PT (also referred to as LPF) were done at CLI, CLI was having problems with their PT ELISA. These problems involved lack of assay sensitivity below 40 to 60 units/ml, use of heat inactivation without prior validation, and problems with quality control. The impact that these problems had on the present PLA were considered minimal for the following reasons. The post booster geometric mean response to PT was 370 units/ml and 471 units/ml for Tripedia™ and ActHIB™ given separately and combined respectively, and very few had low levels of anti-PT post boost. The CHO cell assay is a functional assay for PT antibodies, and this assay also showed no differences between the vaccines given separately or combined.

In conclusion, comparative studies of ActHIB™ and Tripedia™ administered to children 15 to 20 months of age, given either as separate injections or combined through, reconstitution showed that the safety and immunogenicity profile of the combined vaccine was not different from the vaccines given separately.

VI. ADVISORY PANEL CONSIDERATIONS

Data regarding the safety and immunogenicity of ActHIB™ when reconstituted with CLI DTP were presented and discussed at the October 28, 1992 Vaccines and Related Biological Products Advisory Committee meeting. Data on use of Tripedia™ to reconstitute ActHIB™ were not formally presented to the Advisory Committee.

Table 2: Frequency (and Percentages with 95% Confidence Intervals) for Local Reactions 0-72 Hours Post-vaccination

Local Reactions	0-6 hrs	6-24 hours	24-48 hours	48-72 hours
Number of Subjects	856	856	856	856
Any Local Reaction	308 (36.0) (32.8, 39.2)	165 (19.3) (16.7, 21.9)	72 (8.4) (6.5, 10.3)	27 (3.2) (2.0, 4.4)
Erythema <1"	90 (10.6) (8.5, 12.7)	64 (7.5) (5.7, 9.3)	35 (4.1) (2.8, 5.4)	10 (1.2) (0.5, 1.9)
Erythema >1"	5 (0.6) (0.1, 1.1)	10 (1.2) (0.5, 1.9)	3 (0.4) (0.0, 0.8)	0 (0.0) (-)
Swelling/Hardness	66 (7.7) (5.9, 9.5)	63 (7.4) (5.6, 9.2)	34 (4.0) (2.7, 5.3)	15 (1.8) (0.9, 2.7)
Tenderness upon Touch	226 (26.4) (23.4, 29.4)	97 (11.4) 9.3, 13.5)	31 (3.6) (2.4, 4.8)	12 (1.4) (0.6, 2.2)
Pain / Soreness	137 (16.0) (13.5, 18.5)	47 (5.5) (4.0, 7.0)	13 (1.5) (0.7, 2.3)	5 (0.6) (0.1, 1.1)

Table 3: Frequency (and Percentages with 95% Confidence Intervals) for Systemic Reactions 0-72 Hours Post-vaccination

Systemic Reactions	0-6 hrs	6-24 hours	24-48 hours	48-72 hours
Number of Subjects	838	836	834	825
Fever				
38.0 - 38.9 C	118 (14.1) (11.7, 16.5)	63 (7.5) (5.7, 9.3)	37 (4.4) (3.0, 5.8)	20 (2.4) (1.4, 3.4)
39.0 - 39.9 C	8 (1.0) (0.3, 1.7)	1 (0.1) (0, 0.3)	2 (0.2) (0, 0.5)	5 (0.6) (0.1, 1.1)
40.0 - 42.0 C	1 (0.1) (0*, 0.3)	0 (0.0) -	1 (0.1) (0, 0.3)	1 (0.1) (0, 0.3)
Number of Subjects	855	855	855	855
Irritable	296 (34.6) (31.4, 37.8)	164 (19.2) (16.6, 21.8)	91 (10.7) (8.6, 12.8)	56 (6.5) (4.8, 8.2)
Tired	263 (30.8) (27.7, 33.9)	117 (13.7) (11.4, 16.0)	61 (7.1) (5.4, 8.8)	42 (4.9) (3.5, 6.3)
Anorexia	78 (9.1) (7.2, 11.0)	49 (5.7) (4.1, 7.3)	36 (4.2) (2.9, 5.5)	27 (3.2) (2.0, 4.4)
Vomiting	5 (0.6) (0.1, 1.1)	4 (0.5) (0.0, 1.0)	15 (1.8) (0.9, 2.7)	7 (0.8) (0.2, 1.4)
Unusual Cry	5 (0.6) (0.1, 1.1)	3 (0.4) (0.0, 0.8)	2 (0.2) (0, 0.5)	3 (0.4) (0.0, 0.8)
Crying > 3 hours	2 (0.2) (0, 0.5)	0 (0.0) -	0 (0.0) -	0 (0.0) -
Hypotonic / Hyporesponsive	0 (0.0) -	0 (0.0) -	0 (0.0) -	0 (0.0) -

* Confidence Interval limits <0 have been truncated to 0.

Table 4A U93-3109-01
Combined Vaccine vs. Separate Injections: Immune Response to PRP

	Pre-dose		Post-dose	
Group	Combined	Separate	Combined	Separate
n	88	94	93	98
GM (µg/ml)	0.9	1.2	90.3	80.9
% ≥ 0.15 µg/ml	87.5	92.6	100	100
% ≥ 1 µg/ml	45.5	53.2	100	100

No statistical difference between groups (p>0.05).

Table 4B U93-3109-01
Combined Vaccine (C) vs. Separate Injections (S): Immune Response to Diphtheria, Tetanus and Pertussis

	GM Pre-Dose		GM Post-Dose		% 4x Rise	
Group	C	S	C	S	C	S
n	92-93	100-103	93	98	91-92	96-98
Diphtheria Antitoxin (units/ml)	0.148	0.155	6.31	6.65	98.9	97.9
Tetanus Antitoxin (equivalents/ml)	0.052	0.057	0.099	0.145	97.8	96.9
Pertussis:						
Anti-LPF (ELISA units/ml)	26.2	24.6	471.0	369.9	87.0	85.7
Anti-LPF (CHO Cell)	33.5	31.8	806.7	701.6	92.3	90.6
Anti-FHA (ELISA units/ml)	3.83	3.61	44.68	39.81	68.5*	80.6

* Vaccine groups statistically significantly different at p<0.05

Table 5A U93-3109-01 Part 2
Additional Combined Vaccine Lots: Immune Response to PRP

	Pre-dose		Post-dose	
Lot #	4J91/4B	4J92/4L	4J91/4B	4J92/4L
n	66	69	67	68
GM (µg/ml)	0.6	0.6	80.1	73.6
% ≥ 0.15 µg/ml	78.8	73.9	100	100
% ≥ 1 µg/ml	30.3	39.1	100	98.5

No statistical difference between groups (p>0.05)

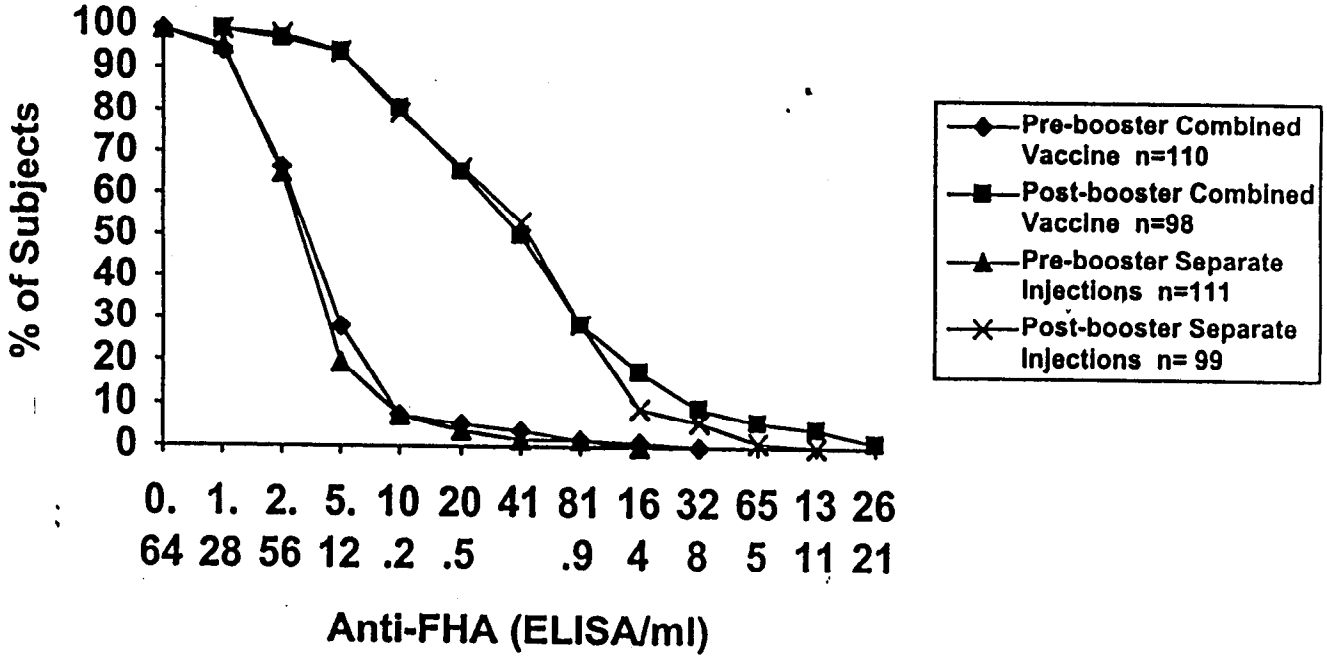
Table 5B U93-3109-01 Part 2
Additional Combined Vaccine Lots: Immune Response to Diphtheria, Tetanus and Pertussis

	GM Pre-Dose		GM Post-Dose		% 4x Rise	
Lot #	4J91/4B	4J92/4L	4J91/4B	4J92/4L	4J91/4B	4J92/4L
n	66-67	69	67	68-69	66-67	69
Diphtheria Antitoxin (units/ml)	0.11	0.14	7.74	8.13	100	98.6
Tetanus Antitoxin (equivalents/ml)	0.046	0.039	0.811	0.767	98.5	97.1
Pertussis:						
Anti-LPF (ELISA units/ml)	9.9[a]	14.7	133.3[b]	224.9	89.4	87.0
Anti-LPF (CHO Cell)	25.75	33.31	266.8[b]	595.3	73.1	85.5
Anti-FHA (ELISA units/ml)	3.24	3.63	43.2	54.5	83.3	87.0

a, b Statistically different from 4J92/4L at p<0.01, p<0.05 respectively

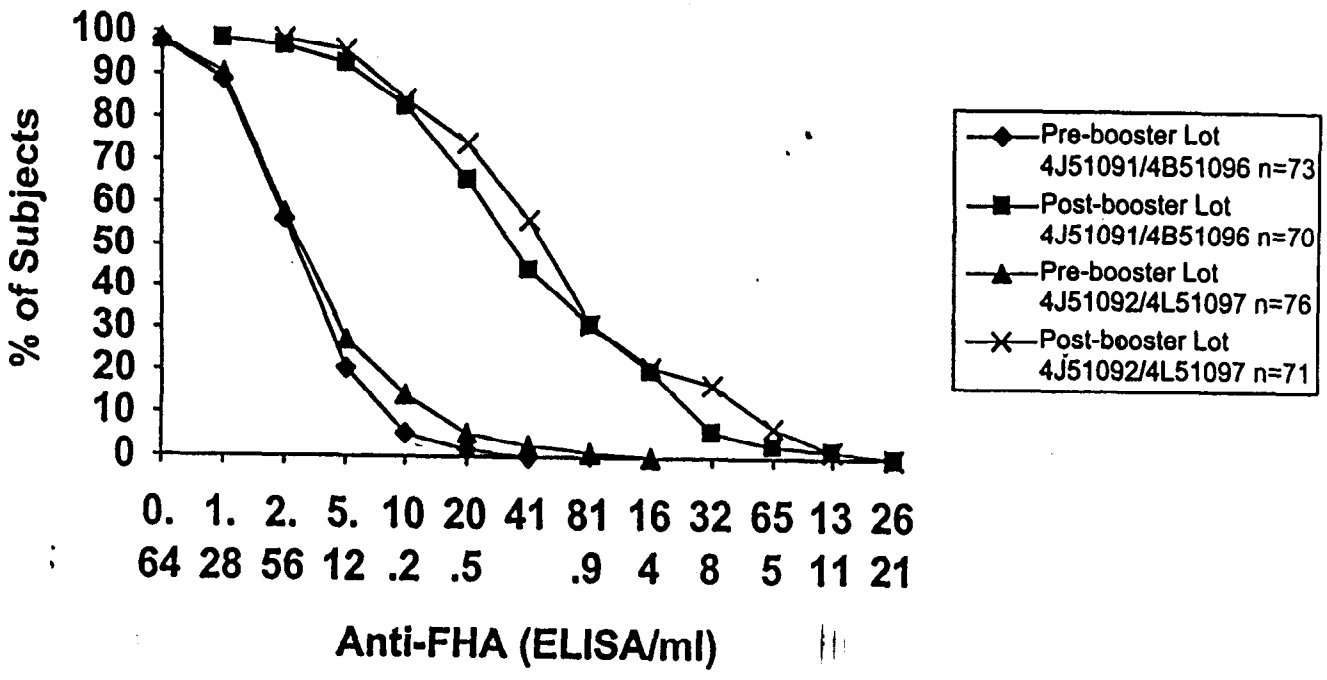
Tripedia®/ActHib® in 15-20 Month Old Children
Protocol U93-3109-01 Part 1

Figure 1. Reverse Cumulative Percentage of Subjects - FHA



Tripedia®/ActHib® in 15-20 Month Old Children
Protocol U93-3109-01 Part 2

Figure 9. Reverse Cumulative Percentage of Subjects - FHA



VII. APPROVED PACKAGE INSERT

Approved package inserts for ActHIb™ and Tripedia™ are attached. The labeling are appropriate and adequate for the products.

Carl Frasch, Ph.D., Chair

Roberta Shahin, Ph.D.

Margaret P. Mitrane, M.D.
For Margaret M. Mitrane

Henry S.H. Hsu, Ph.D.

Lydia Falk, Ph.D., Regulatory Coordinator

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