Summary Basis for Approval

Reference No.: 90-0353

Proper Name: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed

Trade Name: Tripedia™

Manufacturer:
Connaught Laboratories, Inc.

Research Foundation for Microbial Diseases of Osaka University (BIKEN)

The vaccine, Tripedia™, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed, for intramuscular use, is a sterile solution of diphtheria and tetanus toxoids adsorbed, with acellular pertussis vaccine in an isotonic sodium chloride solution containing sodium phosphate to control pH. The acellular pertussis component contains two *Bordetella pertussis* antigens, filamentous hemagglutinin (FHA), and inactivated pertussis toxin (PT). Pertussis toxin (PT) has also been called "lymphocytosis promoting factor", (LPF).

I. Indications and Usage:

Tripedia™ is indicated as a fourth and/or fifth dose for immunization of children 15 months to 7 years of age (prior to seventh birthday) who have previously been immunized against diphtheria, tetanus and pertussis with three or four doses of Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Adsorbed (whole-cell pertussis DTP vaccine).

This product is not recommended for use in children below 15 months of age.

Children who have recovered from culture-confirmed pertussis need not receive further doses of a pertussis-containing vaccine. This vaccine is intended for active immunization against diphtheria, tetanus, and pertussis, and is not to be used for treatment of actual infection.

If a contraindication to the pertussis vaccine component occurs, Diphtheria and Tetanus Toxoids for pediatric use, (DT), should be substituted for each of the remaining doses.

As with any vaccine, vaccination with Tripedia™ may not protect 100% of susceptible individuals.

II. Dose and Route of Administration:

After shaking, Tripedia™ is a homogeneous white suspension. The vaccine is for intramuscular injection only. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

Administration of Tripedia™ may be used as a substitute for whole-cell pertussis DTP for the fourth and/or fifth doses in the immunization series against diphtheria, tetanus and pertussis diseases in children 15 months of age up to 7 years of age (prior to seventh birthday) who have previously received three or four doses of whole-cell DTP vaccine. Each 0.5 mL dose is formulated to contain 6.7 Lf units of diphtheria toxoid, 5 Lf units of tetanus toxoid, and 7.5 µg protein nitrogen (46.8 µg protein) of pertussis antigens. This is presented in the vaccine as approximately 23.4 µg each of inactivated pertussis toxin (PT) and filamentous hemagglutinin

(FHA) protein. Tripedia™ is packaged in 7.5 mL multi-dose vials, containing thimerosal (mercury derivative) as a preservative, at a final concentration of 1:10,000.

III. Manufacturing and Controls:

A. Manufacturing:

Acellular Pertussis Vaccine Concentrate (For Further Manufacturing Use) is manufactured and provided to Connaught Laboratories, Inc. (CLI), by the Research Foundation for Microbial Diseases of Osaka University under a shared manufacturing agreement. The concentrate is combined with previously adsorbed diphtheria and tetanus toxoid pools manufactured at Connaught Laboratories, Inc. of Swiftwater, PA. The combined pertussis concentrate and diphtheria and tetanus toxoid pools are brought to final volume with buffered physiologic saline, and thimerosal is added as a preservative.

The acellular pertussis vaccine component is isolated from culture fluids of phase I *Bordetella pertussis* grown in a modified Stainer-Scholte Medium, and purified by salt precipitation, ultracentrifugation and ultrafiltration. After purification, pertussis toxin (PT) and filamentous hemagglutinin (FHA) are combined to obtain a 1:1 ratio and treated with formaldehyde to inactivate PT. The purity of the pertussis component is ascertained by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and endotoxin content is measured. Thimerosal is added as a preservative. Concentrate vaccine is transported to Connaught under controlled refrigeration.

The diphtheria and tetanus toxoids are produced by growing *Corynebacterium diphtheriae* in a modified Mueller and Miller medium and *Clostridium tetani* in a peptone based medium. After detoxification, the toxoids are separately purified by serial ammonium sulfate fractionation and diafiltration. The toxoids are adsorbed to aluminum potassium sulfate (alum). The adsorbed diphtheria and tetanus toxoids are combined with acellular pertussis concentrate, and diluted to final volume using sterile phosphate-buffered physiologic saline. Thimerosal (mercury derivative) 1:10,000 is added as a preservative. Each 0.5 mL dose contains, by assay, not more than 0.170 mg of aluminum, and 100 µg (less than or equal to 0.02%) of residual formaldehyde.

Each 0.5 mL dose is formulated to contain 6.7 Lf units of diphtheria toxoid and 5 Lf units of tetanus toxoid (both toxoids induce not less than 2 units of antitoxin per ml in the guinea pig potency test), and 7.5 µg of pertussis antigens, expressed as protein nitrogen. This is represented in the final vaccine as approximately 23.4 µg each of inactivated PT and FHA protein.

The adsorbed vaccine, as finished product, is tested for diphtheria and tetanus potency in guinea pigs and for pertussis potency as measured by the ability of the vaccine to induce antibodies to PT and FHA in mice. The vaccine is assayed for the presence of active PT using the histamine-sensitizing factor (HSF) test in mice. Thimerosal, aluminum and free formaldehyde content, sterility and general safety are determined. The identity of the diphtheria and tetanus components is confirmed by a flocculation test with specific antisera and the identity of the pertussis component is confirmed by a dot blotting procedure using specific antisera. The vaccine contains gelatin and polysorbate 80 which are used in the manufacturing process.

Tripedia™ is compounded, filled, labeled, packaged, and released by Connaught Laboratories, Inc. The manufacturer submitted vaccine samples from three lots to demonstrate manufacturing consistency. All lots met the release specifications established by the manufacturer.

B. Stability:

Stability studies have been conducted on three lots of Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed (DTaP) vaccine stored in final container. Vaccine samples were stored at either 5°C (recommended storage temperature), 25°C, or 37°C. The stability was evaluated by measuring diphtheria and tetanus potency using the NIH Minimum Requirements procedure, active PT by the histamine-sensitization (HSF) assay, and pertussis immunogenicity in guinea pigs. Diphtheria and tetanus potency of the 3 lots remained stable for at least 33 months at 5°C, at least 6 months at 25°C, and at least 4 weeks at 37°C. The 3 lots passed the HSF test after storage at 5°C for at least 24 months, at 25°C for at least 12 months, and at 37°C for at least 4 weeks. The pertussis component retained immunogenicity as assessed in a non-quantitative guinea pig immunogenicity test for at least 24 months at 5°C, at least 6 months at 25°C, and at least 4 weeks at 37°C. Results from these ongoing stability studies indicates that the stability profile of DTaP is similar to that for conventional whole-cell pertussis DTP. Consequently, the recommended shelf life for Tripedia™ is not different from that of DTP vaccine. Specifically, the recommended expiration date is 30 months from the date of manufacture when stored at 2-8° C. This includes one year in manufacturer's cold storage and an additional 18 months. The date of manufacture is defined as the date of the initiation of the earliest valid potency test regardless of which component of the final bulk is tested first. The manufacturer has agreed to continue long-term stability studies which will include assessment of pertussis potency using a standardized mouse immunogenicity test.

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 container and package labeling and package insert have been reviewed and were found to be in compliance with the appropriate sections 610.60, 610.61, 610.62, 201.56, and 201.57 of 21 CFR.

The package insert includes statements concerning the vaccine description, individual components, use of the product, immunogenicity experience, contraindications, warnings, precautions, adverse reactions, dosage and administration, how the product is supplied, and information on the storage of the product.

The trade name Tripedia™ is not in conflict with any other trade name. The labeling reflects both manufacture of the pertussis concentrate by BIKEN and manufacture of the final product by Connaught Laboratories, Inc.

E. Establishment Inspection:

Connaught Laboratories, Inc. is a licensed manufacturer of biological products, and as such is subject to annual inspection by FDA. A pre-license inspection of the Connaught Laboratories, Inc. was conducted on August 26-28, 1991. The facility, manufacturing protocols, Quality Control laboratory, storage conditions, record keeping (including acellular component shipping records) and all other aspects of manufacturing of the Tripedia™ vaccine product were considered satisfactory and in compliance with applicable regulatory requirements.

Similarly, a pre-license inspection of the manufacturing establishment of the Research Foundation for Microbial Diseases of Osaka University (BIKEN) located in Kanonji, Japan, was conducted April 22-26, 1991, and found production of the acellular pertussis component to be in compliance with all applicable regulatory requirements.

F. Environmental Assessment:

Substances toxic to the environment are not released into the environment. Environmental assessment was filed, reviewed, and a Finding of No Significant Impact was prepared for this product approval for both Connaught Laboratories, Inc., and The Research Foundation for Microbial Diseases of Osaka University (BIKEN). Each company is in compliance with all state, local or governmental requirements of the country in which production occurs.

IV.Pharmacology:

Diphtheria and tetanus toxoids induce production of antitoxin antibodies which protect against the diseases diphtheria and tetanus, respectively. The diphtheria and tetanus toxoids produced by Connaught Laboratories, Inc. have been used extensively in the licensed whole cell vaccine produced and sold by that company.

The pertussis component of Tripedia™ contains two major proteins: inactivated-PT and FHA. This component has been used in a DTP vaccine containing an acellular pertussis vaccine produced by The Research Foundation for Microbial Diseases of Osaka University (BIKEN) that has been used in Japan since 1981.

The manufacturer's labeling is adequate with respect to pharmacology. No pharmacokinetic or toxicology studies have been done specifically with this vaccine.

V. Medical:

A. General Information

Diphtheria is primarily an intoxication caused by diphtheria toxin, an extracellular protein metabolite of toxinogenic strains of *Corynebacterium diphtheriae*. The incidence of diphtheria in the U.S. has decreased from over 200,000 cases reported in 1921, before the general use of diphtheria toxoid, to only 15 cases reported from 1980 to 1983 [*MMWR* (1991) 40: RR-10].

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin produced by *Clostridium tetani*. The incidence of tetanus in the U.S. has dropped dramatically with the routine use of tetanus toxoid, remaining relatively constant over the last decade at about 90 cases reported annually.

Pertussis is a highly communicable disease of the respiratory tract [*MMWR* (1985) 34: 405-426]. Since immunization against pertussis using the whole cell vaccine became widespread, the number of reported cases and associated mortality in the U.S. has declined markedly [*MMWR* (1970)19: 44; *MMWR* (1990) 39: 57-66].

Acellular pertussis vaccines produced by six different companies have been used in Japan since 1981, primarily in children two years of age and older. With the continued use of those acellular

pertussis vaccines, there has been a decline in disease due to pertussis in Japan [Noble, G.R. et al. (1987) *JAMA* 257: 1351-1356]. One of the Japanese acellular pertussis vaccines is manufactured by The Research Foundation for Microbial Diseases of Osaka University (BIKEN). This pertussis vaccine contains two *B. pertussis* antigens in equal proportions, PT (pertussis toxin, inactivated), and FHA (filamentous hemagglutinin). The BIKEN pertussis component is combined with diphtheria and tetanus toxoids manufactured by Connaught Laboratories, Inc. to make Tripedia™.

B. Clinical Studies:

General summary of clinical evaluation: The efficacy of the BIKEN acellular pertussis component (APC) was studied in a field trial in Sweden conducted in 1986-87. The vaccine was evaluated as a aluminum adsorbed acellular pertussis vaccine called JNIH-6. APC for JNIH-6 was produced by purification of PT and FHA from culture supernatant fluids of *B. pertussis* grown in stationary culture in Roux bottles and inactivated by exposure to formalin for 25 days. US clinical studies were conducted using DTaP vaccine; the BIKEN APC combined with Connaught's diphtheria and tetanus toxoids adsorbed to alum. BIKEN APC used in US trials was produced in either 3000 L or 15000 L fermentors and inactivated by 50 days of formalin exposure. All vaccine for marketing in the US will be produced in the 15000 L fermentor.

To demonstrate efficacy of DTaP (to be marketed under the trade name Tripedia™), laboratory and clinical studies were conducted to demonstrate that JNIH-6 was effective in preventing pertussis, that APC used in JNIH-6 was equivalent to that in DTaP when evaluated by available technology, that the longer period of inactivation did not reduce immunogenicity, and that the antibody response in US children receiving the vaccine as a fourth or fifth dose was comparable to that observed in Swedish children enrolled in the efficacy trial.

Additional US clinical studies compared the safety and immunogenicity of DTaP to that of Connaught Laboratories, Inc. licensed DTP vaccine containing a whole-cell pertussis component.

1. Vaccine comparability studies:

To demonstrate that the BIKEN APC used in JNIH-6 was equivalent to that in DTaP, pre-detoxification material was studied in the laboratory. The equivalence of APC was examined by direct comparison of 3 lots each of pre-detoxification material produced by the Roux method (as was used for JNIH-6), the 3000 L fermentor method, and the 15000 L fermentor method. All three production methods used the same strain of *B. pertussis*. No laboratory test or clinical response has been shown to correlate with or predict clinical efficacy of acellular pertussis vaccines; therefore the physical-chemical, biological, immunochemical, and immunological properties of the nine preparations were evaluated extensively. The nine preparations were indistinguishable by all tests applied. These included PT/FHA ratio, histamine-sensitizing activity, leukocytosis-promoting activity, hemagglutinating activity, SDS-PAGE, acid-PAGE, immunoblotting against two anti-PT and one anti-FHA monoclonal antibodies, and immunoblotting against post-immunization sera from 10 US infants immunized with 3 doses of DTaP, 6 US children receiving whole-cell pertussis DTP as a fourth dose, 8 US children receiving DTaP as a fourth dose, and 12 Swedish infants immunized with JNIH-6 as part of the efficacy trial. Therefore, by available technology, the pre-detoxification starting material for all BIKEN acellular pertussis vaccines can be considered equivalent.

The detoxification process for all of the tested BIKEN acellular pertussis vaccines is identical with the exception that the period of exposure to formalin was extended from 25 to 50 days. The longer inactivation process was employed to reduce the amount of biologically active PT. Data was submitted from a clinical trial conducted in Japan to demonstrate that immunogenicity of the vaccine was not reduced by the longer detoxification process. The clinical trial used 2 lots of DTP

vaccine produced by BIKEN containing the diphtheria and tetanus toxoid components produced by BIKEN. For both lots, the APC was produced by BIKEN using the 3000 L fermentor process. The APC that was used to produce DTaP lot 22 was detoxified by 25 days of exposure to formalin, and the APC for lot 23 was detoxified for 50 days. Immunogenicity results are presented in Table 1. The study was conducted in Japan and compared the antibody response to PT and FHA in infants. The infants received the first dose at 2 months of age, a second dose approximately 6 weeks later, and a third dose 6 months after the second dose. Antibodies were evaluated in serum samples collected before the first immunization, 4 weeks after the second dose, before the third dose, and 4 weeks after the third dose. Results are presented for those infants who lacked antibody in the pre-immunization sample. No significant difference was observed between the groups for any of the assays. Additional studies at Connaught demonstrated that vaccine lots 22 and 23 were similar when tested in the mouse immunogenic potency assay.

Table 1: Comparison of immunogenicity of lots produced by 25 day (lot 22) vs. 50 day (lot 23) inactivation.

			Geometric Mean			
Assay	Lot	N	Pre-1st	Post-2nd	Pre-3rd	Post-3rd
PT-IgG*	Lot 22	24	0.62	55.79	37.53	155.86
(ELISA units/ml)	Lot 23	41	0.82	47.04	30.06	127.12
FHA-IgG*	Lot 22	24	1.20	17.22	12.89	57.89
(ELISA units/ml)	Lot 23	41	1.95	19.41	14.98	59.49
CHO-cell titer#	Lot 22	15	ND§	ND	ND	385
	Lot 23	15	ND	ND	ND	368

* Assays performed at BIKEN on sera from children having no antibody in pre-immunization sample
\# CHO-cell assay performed at Connaught on 15 sera having sufficient volume remaining for assay
§ ND = not determined

2. Efficacy studies:
A large placebo-controlled efficacy trial of the BIKEN acellular pertussis vaccine called JNIH-6 was conducted in Sweden in 1986-87. JNIH-6 contained the two-component PT/FHA shown above to be comparable to the APC contained in Tripedia™. In its first phase, the trial in Sweden was a randomized, double-blinded prospective trial using standardized case definition and active case surveillance. In this phase, 1389 children, 5 to 11 months of age at enrollment, received two doses of JNIH-6 seven to 13 weeks apart and 954 received a placebo control vaccine. During the 15 months of follow-up beginning 30 days after the second dose of vaccine, culture-confirmed whooping cough (defined as cough with positive culture of *B. pertussis*) occurred in 40 placebo and 18 JNIH-6 recipients. The point estimate of protective efficacy was 69% (95% confidence interval: 47 to 82%) for all cases and 80% (95% confidence interval: 59 to 91%) for culture-confirmed cases with cough of over 30 days duration.

Longer term efficacy for vaccine JNIH-6 was evaluated by following the trial children for an additional three years. During this unblinded phase, a passive case reporting system was employed. In this phase, the efficacy was estimated to be 77% (95% confidence interval: 64 to 85%) for all culture-verified cases of pertussis, and 92% (95% confidence interval: 83 to 96%)for all culture-verified case with cough of over 30 days duration.

3. Comparative immunogenicity (US vs Sweden)
The BIKEN PT/FHA vaccine was demonstrated to have some degree of protective efficacy when used in Swedish infants and Tripedia™ was shown (part 4 below) to be immunogenic in US children when used as a fourth dose in children who had previously received three doses of licensed DTP or when used as a fifth dose in children who had previously received four doses of licensed DTP. To bridge these studies, it was necessary to demonstrate that the antibody response was similar in the two populations. A comparison of the antibody responses to PT and FHA in the two populations is shown in Table 2. Samples were collected approximately 8 weeks post-immunization in the Swedish study and 4 weeks post-immunization in the US trial. The antibody concentrations observed in the US children were comparable to those observed in the Swedish population, although the role of antibodies in clinical protection is not known at this time.

Table 2: Comparison of post-immunization antibodies in children from US trials of Tripedia™ to that observed in infants from the efficacy trial in Sweden. All assays performed at Connaught.

	Geometric mean		
	15-20 month olds (US) (N = 354)	4-6 year olds (US) (N = 211)	Swedish infants (N = 40)
PT-IgG (ELISA units/ml)	443	408	162
FHA-IgG (ELISA units/ml)	65	362	79
CHO-cell titer	300	210	187

4. US Comparative studies (comparison of Tripedia™ to Connaught Inc. whole-cell DTP vaccine)

In the United States, BIKEN APC was combined with Connaught's adsorbed diphtheria and tetanus toxoids to create the DTaP vaccine tested clinically by Connaught Laboratories, Inc. Clinical trials in the United States were limited to safety and immunogenicity, and involved more than 6,000 children between 2 months and five years of age. In those U.S. trials, pertussis vaccine produced by both 3,000 liter fermenter technology and by scaled-up 15,000 liter technology, were tested.

Safety and immunogenicity of Tripedia™ compared to CLI's licensed DTP was examined in two studies. The first was in 15- 20 month old children who had previously received 3 doses of DTP and the second was in 4-6 year-old children who had previously received 4 doses of DTP. Immunogenicity results from these studies are shown in Table 3 and safety data in Table 4. Adequate responses to the diphtheria and tetanus components were observed in the US immunogenicity studies.

Table 3: Comparison of IgG antibody to PT and FHA and CHO-cell assay neutralization titers induced by Tripedia or Connaught's licensed DTP in children 15 to 20 months of age and 4 to 6 years of age.

Assay	Age group	Vaccine	N	Pre GMT	Post GMT	% with ≥4-fold increase
PT-IgG	15-20 month	Tripedia	354	14.5	443**	91.5**
(ELISA)	15-20 month	DTP	175	14.5	67	50.3
	4-6 years	Tripedia	211	14.5	408**	89.1**
	4-6 years	DTP	65	15.2	81	55.4
FHA-IgG	15-20 month	Tripedia	354	7.0	65**	73.2**
(ELISA)	15-20 month	DTP	175	6.0	19	34.9
	4-6 years	Tripedia	211	18.9	362**	87.2**
	4-6 years	DTP	65	19.2	104	55.4
CHO-cell	15-20 month	Tripedia	354	25.3	300**	79.9**
titer	15-20 month	DTP	175	24.8	119	62.3
	4-6 years	Tripedia	211	23.6	210**	69.7*
	4-6 years	DTP	65	27.9	107	50.8

* $p < 0.01$, Tripedia vs DTP
** $p < 0.001$, Tripedia vs. DTP

Table 4: Frequency (%) of adverse events occurring within 3 days of administration of either Tripedia or Connaught's licensed DTP in 15 to 20 month old or 4 to 6 year old children. *NOTE:* This table presents the percentage of children for whom the adverse event was reported anytime within the 72 hour period following immunization. Manufacturer's summary in the package insert lists the percentage who reported the event at the 24, 48, and 72 hour timepoints after immunization.

	Frequency (%) of event			
	15 to 20 month olds		4 to 6 year olds	
EVENT:	Tripedia (N = 372)	DTP (N = 189)	Tripedia (N = 240)	DTP (N = 76)
LOCAL REACTIONS				
Tenderness	14.2**	77.2	46.2**	93.4
Erythema	18.3**	28.6	31.3**	60.5
Erythema > 1 inch	2.7**	13.2	17.9**	47.4
Swelling	10.8**	39.7	27.9**	59.2
Swelling > 1 inch	1.7*	13.5	NR§	NR
SYSTEMIC REACTIONS				
Fever > 101°F	4.7**	22.0	4.8	3.0
Irritability	21.2**	68.3	15.8**	44.7
Drowsiness	12.4**	32.8	15.0**	32.9
Anorexia	7.8**	28.6	5.4**	25.0
Vomiting	2.2	3.2	1.7	1.3
High pitched cry	1.1*	3.7	0.0	0.0
Persistent cry	0.3	1.6	0.0	0.0

* $p < 0.05$, Tripedia vs. DTP
** $p < 0.001$, Tripedia vs. DTP
§ NR = not reported

5. Additional safety data:

Three other studies were conducted to collect additional safety data for Tripedia™. The studies were as follows:

a. Large scale safety trial of Tripedia™ in children 15 to 20 months of age. This was an open label safety trial in children who had previously received 3 doses of DTP. In this study, 2873 children received Tripedia™ in combination with other appropriate childhood immunizations. For all study children, local and systemic adverse events were evaluated for at least 30 days and all hospitalizations were monitored for 12 months. Local and systemic reactions occurring within 3 days of immunization were similar to those observed in the safety and immunogenicity trial shown above in Table 4. Full 12 month follow-up data is available for 2442 children. In this trial, there were 20 reports (0.7%) of unusual or high-pitched crying, 9 reports (0.3%) of persistent (> 3 hours) crying, and no reports of any of the following: hypotonic-hyporesponsive episodes, seizures within 7 days of immunization, fever > 105°F within 72 hours, deaths, encephalopathy, or anaphylaxis. In the study population, there were two apparent seizures with unknown relationship to vaccine; both were apparent febrile seizures occurring 9 or 10 days after immunization with DTaP, MMR, OPV, and Hib. Both children recovered fully. Seizures were reported in two other study children; these occurred more than 3 months after immunization and for these no relationship to immunization was indicated. One child developed a severe systemic bacterial infection. Forty-one (41) days post-vaccination, this child developed a bronchopnuemonia with a positive blood culture for *Streptococcus pneumoniae*. The child recovered after appropriate antibiotic therapy.

b. Safety of Tripedia™ compared to Connaught's licensed DTP in infants receiving primary immunization at 2, 4, and 6 months of age. In this study, 285 infants were immunized with Tripedia™ and 95 children were immunized with DTP. Local reactions were evaluated for a total of 1110 injections of Tripedia™ and systemic reactions were evaluated for 930 injections of Tripedia™. Local reactions following Tripedia™ were significantly ($p < 0.001$) lower than DTP for any reaction, tenderness, any erythema, erythema > 1 inch, any swelling, and swelling > 1 inch. Systemic reactions following Tripedia were significantly ($p < 0.01$) lower than DTP for fever >101°F, irritability, drowsiness, anorexia, vomiting, and unusual cry.

c. Large scale safety trial of Tripedia™ in infants receiving primary immunization at 2, 4, and 6 months of age. This was an open label safety trial in 2651 infants receiving Tripedia™ as primary immunization for diphtheria, tetanus, and pertussis. In this study, children received Tripedia™ in combination with other appropriate childhood immunizations at 2, 4, and 6 months of age. For all study children, severe events including all deaths and hospitalizations were evaluated from the day of enrollment until 60 days after the third dose. Partial follow-up is available for 2145 children and complete follow-up has been reported for 1995 of the study children. Reported adverse events that occurred in temporal association with vaccination and which may be considered contraindications to further DTP immunization are listed in Table 5. In the study population, there were three apparent seizures with unknown relationship to vaccine; one child with suspected seizure (duration < one minute) 72 hours following the second dose, a second child with an episode (duration < 3 minutes) 33 days post third dose, and a third child with infantile spasms 52 days following first dose. Two children in the study died of sudden infant death syndrome, one 60 days and the other 185 days after immunization with Tripedia; no relationship to vaccination was indicated. Two children developed a systemic bacterial infection; the first had a positive blood culture for *Haemophilus influenzae* type b 25 days following first dose of Tripedia administered concomitantly with Hib vaccine and OPV, and the second had a positive blood culture for *S. pneumoniae* one month after first dose of Tripedia given concomitantly with OPV. Both children recovered fully after appropriate antibiotic therapy.

Table 5: Reported adverse events that could be considered contraindications* to further DTP immunization that occurred in temporal association with immunization in the infant open label safety trial .

Reported event	Number reported	Percent (≥ 6000 doses)
Persistent/Unusual cry within 48 hours	3	0.05%
Hypotonic-Hyporesponsive Episode within 48 hours	1	0.02%
Fever ≥ 105°F within 48 hours	1	0.02%
Seizures within 72 hours	1§	0.02%

* These events were considered contraindications to further doses of pertussis vaccine before the ACIP revised its recommendations [MMWR (1191) 40:11-28].
§ Possible seizure (duration < one minute) that occurred 72 hours post second dose.

The safety profile of Tripedia was superior to that of licensed DTP vaccine containing a whole-cell pertussis component and was superior to a historical control provided by previous clinical experience with DTP vaccine [Cody et al., (1981) *Pediatrics* 68: 650-660]. Because an insufficient number of children have been followed to determine the frequency of uncommon adverse events associated with immunization, the manufacturer has made a commitment to monitor these through a post-marketing surveillance program.

The examination of serious adverse reactions was important because of the occurrence of a number of deaths from invasive infectious disease in children who had participated in the Swedish efficacy trial. Specifically, three deaths due to invasive bacterial infections occurred among the 1389 infants in the JNIH-6-treated group [Storsaeter et al., (1988) *Pediatr. Infect. Dis.* 7: 637-645]. This observation represented a disproportionate distribution of the deaths. Since deaths associated with invasive bacterial infections are relatively uncommon, and since the trial was not intended, both by its design and by virtue of the numbers of children included in the test group, to discriminate a test group effect for such uncommon events, it appeared unlikely that an association with immunization could be proven or disproven. Investigators concluded that, although the distribution of deaths associated with invasive infectious disease in the Swedish trial groups was disproportionate, there was no evidence of a predisposition in the vaccine-treated children toward infectious disease generally, toward viral or bacterial diseases, or toward hospitalization for infectious disease. Antibiotic use was, likewise, no more prevalent in vaccine-treated children. Ultimately, however, the safety issue raised by the Swedish trial could only be resolved by an expanded clinical evaluation.

This issue was addressed in the U.S. safety trials; all study children in US trials of Tripedia™ were followed to determine the incidence of invasive bacterial infections. To date, there have been no reports of deaths due to invasive bacterial infection in the US studies. There are three reports of culture-confirmed invasive bacterial infections; all children recovered fully following appropriate therapy. For all US trials reported to date, 6137 children have received a total of 11,194 doses of Tripedia™. The frequency of these events in US trials (3 confirmed infections among 6137 children [0.05% of children]) was lower than observed in the Swedish trial (3 deaths due to invasive bacterial infection among the 1389 study children [0.22% of children]). The manufacturer has committed to continue to monitor for occurrences of invasive bacterial infections in its post-marketing surveillance program.

6. Scale-up from 3000 L to 15000 L fermentor.

The comparative safety and immunogenicity trials summarized above were conducted with 3 lots of Tripedia™ using acellular pertussis concentrate (APC) produced by a 3000 L fermentor process. Batches for licensing are produced using a scaled-up (15000 L) cultivation and purification process. Laboratory studies demonstrated that the APC produced by the 3000 L method was equivalent to that produced by the 15000 L method. The inactivation method at BIKEN and the batching at Connaught are unchanged between the 3000 L and 15000 L procedures. Lots produced for commercial distribution using the 15000 L process passed the mouse immunogenic potency assay and histamine-sensitizing test for toxicity using limits established by repetitive testing of the vaccine lots produced by the 3000 L process and evaluated in clinical trials. Confirmation of the safety of the product produced in the 15000 L fermentor was obtained by a secondary analysis of the large scale safety trial in 15 to 20 month old children. The reaction rates were compared in 553 children who received lot 4549 (3000 L method) and 890 children who received lot OM11114 (15000 L fermentor). There was no significant difference in reaction rates between these two lots with the exception of tenderness which was significantly lower ($p < 0.001$) in lot OM11114. Reaction rates for both lots were similar to those observed in the comparative clinical trial summarized in Table 4.

The labeling of the Connaught combined vaccine is inclusive of all adverse reactions encountered in the U.S. trials. A description of the Swedish experience is likewise included.

VI. Advisory Panel Considerations:

Data regarding the manufacture, safety, and efficacy of Tripedia™ were discussed at the Nov. 12, 1991, meeting of the Vaccines and Related Biological Products Advisory Committee.

VII. Approved Package Insert:

A copy of the approved package insert is attached.

Bruce D. Meade, Ph. D., Chairman Michael J. Brennan, Ph. D. Drusilla L. Burns, Ph. D.

Jane L. Halpern, Ph. D. Ghanshyam Gupta, Ph. D. Bascom F. Anthony, M. D.