SUMMARY BASIS OF APPROVAL

REFERENCE NUMBER: 95-1773

DRUG LICENSED NAME: **Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed**

MANUFACTURER: **SmithKline Beecham Biologicals**

DRUG TRADE NAME: **INFANRIX**

The vaccine is a sterile combination of diphtheria and tetanus toxoids (D and T respectively) and three pertussis antigens, inactivated pertussis toxin (PT), filamentous hemagglutinin (FHA) and pertactin (69 kiloDalton outer membrane protein) adsorbed onto aluminum hydroxide.

I. Indications for use

Infanrix is indicated for active immunization against diphtheria, tetanus and pertussis (whooping cough) in infants and children 6 weeks to 7 years of age (prior to seventh birthday). Because of the substantial risks of complications of the disease, completion of a primary series of pertussis vaccine early in life is strongly recommended.

Individuals 7 years of age or older should not receive this vaccine. In such individuals, Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) is preferable to use of either tetanus or diphtheria vaccines alone.

Children who have recovered from culture-confirmed pertussis need not receive further doses of a pertussis-containing vaccine, but should receive additional doses of Diphtheria and Tetanus Toxoids Adsorbed (DT) for pediatric use to complete the series in accordance with ACIP recommendations.

In instances where the pertussis vaccine component is contraindicated, Diphtheria and Tetanus Toxoids Adsorbed (DT) for pediatric use may be substituted for each of the remaining doses.

The decision to administer or delay vaccination because of a current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. All vaccines can be administered to persons with mild illness such as diarrhea, mild upper respiratory infections with or without low-grade fever or other low-grade febrile illness.

Where passive protection is required, Tetanus Immune Globulin and/or Diphtheria Antitoxin may also be administered at separate sites.

As with any vaccine, *Infanrix* may not protect 100% of individuals receiving the vaccine.

This product is not recommended for treatment of actual infections.

II. Dosage Form, Route of Administration and Recommended Dosage

Infanrix is supplied as sterile, turbid, white suspension in single dose vials (packages of 10 vials) ready for use without reconstitution. After removal of the 0.5 mL dose, any vaccine remaining in the vial should be discarded.

Infanrix should be administered by intramuscular injection. The preferred sites are the anterolateral aspects of the thigh or the deltoid muscle of the upper arm. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. This product should not be administered subcutaneously.

Primary Immunization
The primary immunization course for children less than 7 years of age is three doses of 0.5 mL, given intramuscularly, at 4- to 8-week intervals (preferably 8 weeks). The customary age for the first dose is 2 months of age, but it may be given starting at 6 weeks of age and up to the seventh birthday. It is recommended that *Infanrix* be given for all three doses since no interchangeability data on acellular DTP vaccines exist for the primary series. *Infanrix* may be used to complete the primary series in infants who have received one or two doses of whole-cell DTP vaccine. However, the safety and efficacy of *Infanrix* in such infants have not been evaluated.

Booster Immunization
When *Infanrix* is given for the primary series, a fourth dose is recommended at 15 to 20 months of age. The interval between the third and fourth dose should be at least 6 months. At this time, the available data are insufficient to establish frequencies of adverse events following a fifth dose of *Infanrix* in children who have previously received four doses of *Infanrix*.

If a child has received whole-cell DTP vaccine for one or more doses, *Infanrix* may be given to complete the five-dose series. A fourth dose is recommended at 15 to 20 months of age. The interval between the third and fourth dose should be at least 6 months. Children 4 to 6 years of age (up to the seventh birthday) who received all four doses by the fourth birthday, including one or more doses of whole-cell DTP vaccine, should receive a single dose of *Infanrix* before entering kindergarten or elementary school. This dose is not needed if the fourth dose was given on or after the fourth birthday.

III. Manufacturing and Controls

A. Manufacturing

Diphtheria and Tetanus Toxoids adsorbed bulk concentrates for further manufacturing use are produced by Chiron Behring GmbH & Co., Marburg, Germany. The acellular pertussis antigens are manufactured by SmithKline Beecham Biologicals S.A., (SB Bio) Rixensart, Belgium. Formulation, filling, testing, packaging and release of the vaccine are conducted by SB Bio.

Diphtheria toxin is produced by growing *Corynebacterium diphtheriae*, [redacted] strain, in Linggoud and Fenton medium containing bovine extract. Tetanus toxoid is produced by growing *Clostridium tetani*, [redacted] in a modified [redacted] and medium.

Both toxins are detoxified with formaldehyde, concentrated and partially purified by ultrafiltration. Further purification is achieved by [redacted] and sterile filtration. The diphtheria and tetanus toxoids are each adsorbed onto Aluminum hydroxide and [redacted] and [redacted] The final product is tested for potency [redacted], aluminum, formaldehyde, chloride, 2-phenoxyethanol, pH, sterility [redacted] (according to US requirements), specific toxicity [redacted] and potency. The final formulated DT bulk is shipped by Chiron Behring GmbH & Co. to SB Bio in Rixensart, Belgium for the formulation of *Infanrix*.

The three acellular pertussis antigens (pertussis toxin [PT], filamentous hemagglutinin [FHA] and pertactin) are isolated from phase 1 *Bordetella pertussis* culture grown in modified Stainer-Scholte liquid medium. PT and FHA are extracted from the fermentation broth by adsorption on hydroxyapatite gel; pertactin is extracted from the cells by heat treatment and flocculation using barium chloride. These antigens are purified in successive chromatographic steps: PT and FHA by hydrophobic, affinity and size exclusion; pertactin by ion exchange, hydrophobic and size exclusion processes. PT is detoxified using formaldehyde and glutaraldehyde. FHA and pertactin are treated with formaldehyde. Each antigen is individually adsorbed onto aluminum as aluminum hydroxide.

Each 0.5 mL dose of the final vaccine, *Infanrix*, contains, by assay, not more than 0.6 mg aluminum. Each 0.5 mL dose of *Infanrix* is formulated to contain 25 Lf diphtheria toxoid, 10 Lf tetanus toxoid (both toxoids induce at least 2 neutralizing units/mL of serum in the guinea pig potency test), 25 mcg PT, 25 mcg FHA and 8 mcg pertactin. The potency of the pertussis component is evaluated by measurement of the antibody response to PT, FHA and pertactin in immunized mice using an ELISA.

Each 0.5 mL dose also contains 2.5 mg 2-phenoxyethanol as a preservative, 4.5 mg sodium chloride, water for injection, and not more than 0.02% (w/v) of residual formaldehyde. The vaccine contains polysorbate 80 (Tween 80) which is used in the production of the pertussis concentrate. The inactivated acellular pertussis component contributes less than 5 endotoxin units (EU) per 0.5 mL dose.

B. Stability Studies

Stability studies have used 3 lots of DTaP (DTPa801A2, DTPa802A2, and DTPa803A3) filled into single dose vials. The containers were kept at 2°C - 8°C for 24 months followed by an incubation of [redacted] days at [redacted]°C. At the time of approval these lots passed the potency test for D and T [redacted], the lots passed the single dose [redacted] potency test [redacted] CBER conducted a test for pertussis toxin reversion on 802A2, this lot did not show any evidence of reversion.

Additional stability data is available on lots manufactured at [redacted] scale (DTPa116B2, DTPa117B2, DTPa118B2) and stored in single dose vials. This data shows the vaccine to be stable after storage for 36 months at 2°C-8°C. The D and T potency tests were those recommended by the Eu. Ph., the [redacted] potency test was the [redacted] test (the amount of each antigen which induced an immunogenic response in [redacted] of the mice in each group). CBER has tested lot 119A2 for pertussis toxin reversion, this lot did not show any evidence of reversion.

The company requested 36 month dating. The committee felt that although data were available for 24 months storage of the product manufactured at current scale the 36 month data is supportive and thus 30 month dating was granted at time of approval. SKB have committed to submit their stability testing results conducted at 30 and 36 months on lots 801A2, 802A2 and 803A2. They commit to include histamine sensitization test at these time points on these lots. In addition they have committed to include the HST as part of their stability protocol.

For the purpose of stability studies, tests related to the pertussis components are:

[redacted]

C. Validation

All major equipment and analytical methodology have been appropriately validated by SBBio at the Rixensart, Belgium facility and found to be adequate for control and regulatory purposes.

D. Labeling

Labels and labeling have been reviewed for compliance with 21 CFR 610.60, 610.61, 610.62, 201.56 and 201.57 and have been found satisfactory.

E. Establishment Inspection

A pre-license inspection of the SmithKline Beecham Biologicals production facility in Rixensart, Belgium, was conducted June 10-21, 1996. Deviations from Good Manufacturing Practices (GMP) were noted and they were immediately corrected by the manufacturer. The facility is now considered to be in compliance with GMP regulations.

F. Environmental Assessment

In accordance with 21 CFR 25.31a, an environmental assessment was prepared. This was reviewed and a Finding of No Significant Impact was prepeared. No potential adverse environmental impact is expected from the manufacture and use of *Infanrix*.

G. Pharmacology

The manufacturer's labeling is adequate with respect to pharmacology.

V. Medical

A. General Information

Diphtheria usually occurs as membranous nasopharyngitis and/or obstructive laryngotracheitis caused by diphtheria toxin, an extracellular protein metabolite of toxigenic strains of *Corynebacterium diphtheriae*. While the incidence of diphtheria in the United States has decreased from over 200,000 cases reported in 1921, before the general use of diphtheria toxoid, to only 30 cases of respiratory diphtheria reported from 1983 to 1993, the ratio of fatalities to attack rate has remained constant at about 5% to 10%. The highest case fatality rates are in the very young and in the elderly. Diphtheria remains a serious disease in some areas of the world as evidenced by the recent outbreak in the former Soviet Union.

Tetanus is a neurologic disease caused by the neurotoxin produced by *Clostridium tetani*. The incidence of tetanus in the United States has dropped dramatically with the routine use of tetanus toxoid to a record low of 45 cases in 1992. Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus toxin does not occur in the U.S.

Pertussis (whooping cough) is a disease of the respiratory tract caused by *Bordetella pertussis*. Pertussis is highly communicable and can cause severe disease, particularly among the very young. Since immunization against pertussis became widespread, the number of reported cases and associated mortality in the United States have declined from an average annual incidence and mortality of 150 cases and 6 deaths per 100,000 population, respectively, in the early 1940s to annual reported

incidences of 1.6, 2.6 and 1.8 cases per 100,000 population in 1992, 1993 and 1994, respectively. Precise epidemiologic data do not exist, since bacteriological confirmation of pertussis can be obtained in less than half of the suspected cases. Most reported illness from *B. pertussis* occurs in infants and young children in whom complications can be severe. From 1980 to 1989, of 10,749 pertussis cases reported nationally in infants less than 1 year of age, 69% were hospitalized, 22% had pneumonia, 3.0% had seizures, 0.9% had encephalopathy and 0.6% died.

Simultaneous immunization against diphtheria, tetanus and pertussis during infancy and childhood using a conventional whole-cell DTP has been a routine practice in the United States since the late 1940s. It has played a major role in markedly reducing the incidence of cases and deaths from each of these diseases.

Although routine vaccination with whole-cell DTP has significantly reduced pertussis-related morbidity and mortality, whole-cell pertussis vaccines do cause local and systemic adverse events. Concerns regarding reactogenicity of whole-cell DTP have spurred development of safer pertussis vaccines with high efficacy.

Infanrix contains three of the antigenic components of *B. pertussis* believed to contribute to protective immunity including: pertussis toxoid; filamentous hemagglutinin and pertactin. Although the role of individual pertussis antigens in providing protective immunity in humans is not well understood, clinical trials which evaluated candidate acellular DTPs manufactured by SB Bio supported the efficacy of three-component *Infanrix*.

B. Clinical Studies

Clinical trials have been undertaken to assess the safety, immunogenicity, lot-to-lot consistency and protective efficacy of *Infanrix*.

1. Safety

A total of 92,502 doses of *Infanrix* has been administered in clinical trials. In these trials, 28,749 infants have been administered *Infanrix* as a three-dose primary series, 5,830 children have been administered *Infanrix* as a fourth dose following three doses of *Infanrix*, and 22 children have received *Infanrix* as a fifth dose following four doses of *Infanrix*. In addition, 439 children and 169 children have received *Infanrix* as a fourth or fifth dose following three or four doses of whole-cell DTP vaccine, respectively. In comparative studies, *Infanrix* has been shown to cause fewer of the local and systemic adverse reactions commonly associated with whole-cell DTP. However, studies have shown that the rate of erythema, swelling and fever increased with successive doses of *Infanrix*.

In a double-blind, randomized National Institutes of Health (NIH)-sponsored comparative trial in Italy, safety data in a three-dose primary series are available for 4,696 infants who received at least one dose of *Infanrix* and 4,678 infants who received at least one dose of whole-cell DTP manufactured by Connaught Laboratories, Inc. Data were actively collected by parents using standardized diaries for eight consecutive evenings after each vaccine dose with follow-up telephone calls made by nurses after the eighth day. Table 1 lists adverse events reported to occur during the three days after each dose. All common solicited adverse events were less frequent following vaccination with *Infanrix* as compared to whole-cell DTP after each one of the three doses.

A similar reduction in adverse events was seen in a randomized, double-blind, comparative trial conducted in the U.S. when *Infanrix* was compared to two US-licensed whole-cell DTP vaccines. Adverse events were actively solicited utilizing standardized diaries with follow-up

telephone calls made at days 1, 4 and 8 by blinded study personnel. Table 2 summarizes the frequency of adverse events within 3 days of the three primary immunizing doses. The incidence of redness, swelling, pain, fever (rectal temperature >101°F), poor appetite, drowsiness and fussiness were lower following *Infanrix* than following either whole-cell DTP.

The frequency of adverse reactions following each dose in children who received *Infanrix* at 2, 4 and 6 months of age in a U.S. NIH-sponsored trial are shown in Table 3. Of the 120 infants who received the three-dose primary series, a subset of 76 received a fourth dose of *Infanrix* at 15 to 20 months of age. Adverse events were actively solicited using standardized diaries with follow-up telephone calls made at day 3 by blinded study personnel.

Of 22,505 children who had previously received three doses of Infanrix at 3, 4 and 5 months of age in the large safety trial in Germany, 5361 received a fourth dose at 10 to 36 (mean 19.9) months of age. Standardized diaries were available on 2457 children receiving the primary series and 1809 children receiving the fourth dose. Local and systemic reaction rates within 3 days of vaccination for each dose are reported as in Table 4. In this study the rate of erythema, swelling, pain and fever increased with successive doses of Infanrix.

In a double-blind, randomized study conducted in Germany, additional safety data are available from 13-27-month-old children who received *Infanrix* or whole-cell DTP, manufactured by Chiron Behring GmbH & Co, as a fourth dose. These children were previously primed with three doses of the same vaccine. The rates of adverse events, which were actively solicited utilizing standardized diaries, are presented in Table 5.

The incidence of redness, swelling, severe swelling (greater than 2 cm), pain, fever, severe fever (rectal temperature >103.1°F), eating and drinking less than usual, vomiting, drowsiness and unusual crying was lower following vaccination with *Infanrix* as compared to whole-cell DTP vaccine.

Cases of edematous swelling, generally beginning within 48 hours of vaccination and resolving spontaneously over an average of 4 days without sequelae, have been reported with *Infanrix*. In the German study in which 5,361 children received a fourth dose of *Infanrix* after three doses of the same vaccine, swelling of the injected thigh was reported spontaneously in 62 vaccinees (1.2%). This swelling was associated with pain upon digital pressure in 53% of cases, with rectal temperature ≥100.4°F in 45% of cases, and with local redness in 71% of cases (redness of the entire thigh was reported in 17% of cases). The mean difference in the circumference of the thighs in those subjects in whom this was measured (N=17) was 2.2 cm (range: 0.5 to 5 cm). In 1,809 children for whom standardized diaries were available, edematous swelling was observed in 2.5% of vaccinees.

In clinical studies of Infanrix to date, edematous swelling has been seen only with *Infanrix* as a fourth dose in *Infanrix*-primed individuals. In other countries where Infanrix has been licensed, limb swelling has rarely been reported following administration of *Infanrix* at any dose in the series, including the primary series. Edematous swelling has also been reported following administration of other acellular DTP vaccines, acellular pertussis vaccine alone (without DT), whole-cell DTP, and other vaccines.

Table 6 lists the frequency of adverse events in U.S. children who received *Infanrix* (N=110) or whole-cell DTP (manufactured by Lederle Laboratories; N=55) at 15 to 20 months of age and in U.S. children who received *Infanrix* (N=115) or whole-cell DTP (manufactured by Lederle Laboratories; N=57) at 4 to 6 years of age. All children had previously received three or four doses of whole-cell DTP at approximately 2, 4, 6 and 15-18 months of age. Adverse events were actively solicited using standardized diaries with follow-up telephone

calls made at days 1, 4 and 8 by blinded study personnel. Significantly fewer solicited local and general adverse events were reported following *Infanrix* than following whole-cell DTP when administered as the fourth or fifth dose in those previously primed with three or four doses of whole-cell DTP.

Severe Adverse Events
Severe adverse events reported from the double-blind, randomized comparative NIH Italian study involving 4,696 children administered *Infanrix* or 4,678 children administered whole-cell DTP, manufactured by Connaught laboratories, Inc., as a three-dose primary series are shown in Table 7. The incidence of rectal temperature ≥104°F, hypotonic-hyporesponsive episodes and persistent crying ≥3 hours following administration of *Infanrix* was significantly less than that following administration of whole-cell DTP.

In the large German safety trial that enrolled 22,505 infants (66,867 doses of *Infanrix* administered as a three dose primary series) all subjects were monitored for unsolicited adverse events (using report cards) that occurred within 28 days following vaccination. In a subset of subjects (N=2,457) these cards were standardized diaries which solicited specific adverse events that occurred within 8 days of each vaccination in addition to unsolicited adverse events which occurred throughout the course of the entire study (from study enrollment until approximately 30 days following the third vaccination). Cards from the whole cohort were returned at subsequent visits and were supplemented by spontaneous reporting by parents and a medical history after the first and second dose of vaccine. In the subset of 2,457 subjects, adverse events following the third dose of vaccine were reported via standardized diaries and spontaneous reporting at a follow-up visit. Adverse events in the remainder of the cohort were reported via report cards which were returned by mail approximately 28 days after the third dose of vaccine. Adverse events (rates per 1,000 doses) occurring within 7 days including those events deemed by investigators as related as well as those felt to be unrelated to vaccination included: unusual crying (0.09), febrile seizure (0.0), afebrile seizure (0.13) and hypotonic-hyporesponsive episodes (0.01).

Rates of serious adverse experiences that are less common than those reported in the German safety trial are not known at this time.

In clinical trials involving more than 29,000 infants and children, 14 deaths in *Infanrix* recipients were reported. Causes of deaths included nine cases of Sudden Infant Death Syndrome (SIDS) and one of each of the following: meal aspiration, hepatoblastoma, neuroblastoma, invasive bacterial infection and sudden death in a child greater than 1 year of age. None of these events was determined to be vaccine-related. The rate of SIDS observed in the large German safety study was 0.3/1000 vaccinated infants. The rate of SIDS in the NIH-sponsored Italian efficacy trial was 0.4/1000 vaccinated infants. The reported rate of SIDS in the U.S. from 1985 to 1991 was 1.5/1000 live births. By chance alone, some cases of SIDS can be expected to follow receipt of whole-cell or acellular DTP vaccine.

As with any vaccine, there is the possibility that broad use of *Infanrix* could reveal adverse reactions not observed in clinical trials.

2. Immunogenicity

The humoral antibody responses to the five vaccine components were determined by specific ELISA's. The methods used by SB Bio were developed in-house using international reference preparations for calibration.

In the absence of a laboratory or serologic correlate of protection to pertussis, the sponsor was asked to demonstrate that the antibody responses to the pertussis

antigens in US children receiving Infanrix as a three dose primary series were comparable to the responses in Italian and German children immunized in the efficacy studies.

To evaluate the serological responses to immunization the sponsor used an ELISA assay to measure [redacted] antibodies to PT, FHA and 69k in sera from children who had received the vaccine. None of these assays has been shown to correlate with protection.

The sponsor has provided data in the PLA to demonstrate that the ELISA assays used to measure antibody titers to the pertussis components of the vaccine have been comparable throughout the time when these data has been generated. In addition, the sponsor has provided population bridging data to show that the response of US infants to Infanrix is comparable to that of infants in the efficacy studies. Sera obtained one month following the third dose from US children, vaccinated 2, 4 and 6 months; Italian children, vaccinated in the Efficacy Study at 2, 4 and 6 months; and German children, vaccinated at 3, 4 and 5 months, were assayed in the same laboratory at the same time. The sera from the German study were from children who had been vaccinated with the same two lots of vaccine as the US children. The children in the Italian trial were vaccinated with a different lot of vaccine. The results from this study indicate that US infants vaccinated with Infanrix have a comparable immune response to all three pertussis antigens, one month after a three dose primary series, to Italian infants and German infants.

The sponsor has made a manufacturing change in order [redacted] This change has been [redacted] Laboratory characterization data has been provided in the PLA to demonstrate that the antigens produced after this [redacted] are the same as those used to manufacture the lots used in the efficacy trials. In addition, the sponsor has provided clinical data to show that a lot of *Infanrix* made with [redacted] produces a similar antibody response following three primary doses in infancy (administered at 3, 4.5, and 6 months of age) as lots of vaccine made using the former process.

The sponsor has made a commitment to submit data from a clinical immunogenicity study (schedule: [redacted]

Immune response to diphtheria and tetanus components: The sponsor has provided data to the PLA showing that sera obtained 1 month after the primary course were able to neutralize diphtheria toxin using a VERO cell toxin neutralization assay. In 45 sera tested protective titers (≥0.01 antitoxin units/ml of serum) were achieved in 100% of sera. An in vivo mouse toxin neutralization test demonstrated the ability of infant sera (N=45) obtained 1 month after the primary course to neutralize tetanus toxin. Protective titers (≥0.01 antitoxin units/ml of serum) were achieved in 100% of sera tested.

Immune Response of Infanrix *Administered as a Three-Dose Primary Series*
In 5 clinical trials, lot-to-lot consistency with respect to the immunogenicity of Infanrix was assessed following administration of the vaccine as a primary course to infants. When vaccine lots were compared within the same trial, it could be demonstrated that the vaccine response to all three pertussis components in Infanrix was consistent and independent of the vaccine lot used. Responses to the diphtheria and tetanus components were also independent of vaccine lots administered.

Immune Response of Infanrix *Administered as the Fourth Dose of DTP in Children Primed with* Infanrix

In a double blind, randomized study, *Infanrix* was compared with whole-cell DTP (manufactured by Lederle) administered 18 months of age. Children had been previously primed at 2, 4 and 6 months of age with the same vaccine. After the fourth dose, *Infanrix* was found to be more immunogenic than whole-cell DTP for two of the three pertussis antigens (FHA and 69kDa) and as immunogenic for the third pertussis antigen (PT). Anti-diphtheria response after the fourth dose of *Infanrix* or whole-cell DTP was similar. Infants receiving whole-cell DTP had significantly higher GMTs for anti-tetanus following the fourth dose; however, all infants had antibody titers $\geq$ 0.1 IU/mL for both diphtheria and tetanus.

Immune Response of Infanrix *Administered as the Fourth or Fifth Dose of DTP in Children Primed with Whole-cell DTP*

In two U.S. studies in which *Infanrix* was administered to infants 15 to 20 months old or to children 4 to 6 years old as the fourth or fifth dose of DTP, respectively, and compared to U.S. licensed DTP in children who were primed with whole-cell DTP, those receiving *Infanrix* had significantly higher GMTs to anti-PT, anti-FHA and anti-pertactin than those receiving whole-cell DTP. No differences were observed in the GMTs to diphtheria or tetanus toxoids between the two groups in either study.

3. Efficacy

Infanrix has been shown to be effective in preventing WHO-defined pertussis in two published clinical trials conducted in Italy and Germany when administered as a primary series.

A double-blind, randomized, placebo-controlled (DT) trial conducted in Italy, sponsored by the National Institutes of Health (NIH), assessed the absolute protective efficacy of *Infanrix* when administered at 2, 4 and 6 months of age. A total of 15,601 infants were immunized with one of two tri-component acellular DTP vaccines (containing inactivated PT, FHA and pertactin), or with whole-cell DTP vaccine manufactured by Connaught Laboratories, Inc., or with DT vaccine alone. The mean length of follow-up was 17 months, beginning 30 days after the third dose of vaccine. The population used in the primary analysis of vaccine efficacy included 4,481 *Infanrix* vaccinees, 4,348 whole-cell DTP vaccinees and 1,470 DT vaccinees. After three doses, the protective efficacy of *Infanrix* against WHO-defined typical pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing) was 84% (95% CI: 76% to 89%) while the efficacy of the whole-cell DTP vaccine was 36% (95% CI: 14% to 52%). When the definition of pertussis was expanded to include clinically milder disease with respect to type and duration of cough, with infection confirmed by culture and/or serologic testing, the efficacy of *Infanrix* was calculated to be 71% (95% CI: 60% to 78%) against >7 days of any cough and 73% (95% CI: 63% to 80%) against $\geq$14 days of any cough. A longer follow-up showed that after three doses the absolute efficacy of *Infanrix* remained high against WHO-defined pertussis at 78% (95% CI: 62% to 87%) in children whose average age was then 33 months (20-39 months).

A prospective, blinded efficacy study was also conducted in Germany employing a household contact study design. In preparation for this study, three doses of *Infanrix* were administered at 3, 4 and 5 months of age to more than 22,000 children living in six areas of Germany in a large safety and immunogenicity trial. Infants who did not participate in this trial could have received whole-cell DTP vaccine (manufactured by Behringwerke A.G., Germany) or DT vaccine. Pediatricians were asked to monitor households with a first potential case (index case) of typical pertussis which was identified by spontaneous presentation to a physician. Households were enrolled in the study if there was at least one

other household member (a household contact) 6 to 47 months of age. Prospective follow-up of household contacts of index cases for the incidence and progression of pertussis was performed by a separate physician who was blinded to the vaccination status of the household. Calculation of vaccine efficacy was based on attack rates of pertussis in household contacts classified by vaccination status. Of the 173 unvaccinated household contacts, 96 developed WHO-defined pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing), as compared to 7 of 112 contacts vaccinated with *Infanrix* and 1 of 75 contacts vaccinated with whole-cell DTP vaccine. The protective efficacy of *Infanrix* was calculated to be 89% (95% CI: 77% to 95%), with no indication of waning of protection up until the time of the booster. The protective efficacy of whole-cell DTP vaccine was calculated to be 98% (95%CI: 83% to 100%). The average age of *Infanrix* vaccinees at the time of follow-up in this trial was 13 months (range 6-25 months). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of *Infanrix* against ≥7 days of any cough was 67% (95% CI: 52% to 78%) and against ≥ 7 days of paroxysmal cough was 81% (95% CI: 68% to 89%). The corresponding efficacy rates of *Infanrix* against ≥14 days of any cough or paroxysmal cough were 73% (95% CI: 59% to 82%) and 84% (95% CI: 71% to 91%), respectively.

Efficacy of the diphtheria toxoid used in *Infanrix* was determined on the basis of immunogenicity studies, with a comparison to a serological correlate of protection (0.01 antitoxin units/mL) established by the Panel on Review of Bacterial Vaccines and Toxoids. A VERO cell toxin neutralizing test confirmed the ability of German infant sera (N=45), obtained 1 month after the primary course, to neutralize diphtheria toxin. Protective titers (≥0.01 antitoxin units/mL of serum) were achieved in 100% of the sera tested.

Efficacy of the tetanus toxoid used in *Infanrix* was determined on the basis of immunogenicity studies with a comparison to a serological correlate of protection (0.01 antitoxin units per mL) established by the Panel on Review of Bacterial Vaccines and Toxoids. An in vivo mouse toxin neutralizing test confirmed the ability of US infant sera (N= 45) obtained 1 month after the primary course, to neutralize tetanus toxin. Protective titers (≥0.01 antitoxin units/mL of serum) were achieved in 100% of the sera.

4. Other Clinical Studies

Concomitant Vaccine Administration
In clinical trials, *Infanrix* was routinely administered, at separate sites, concomitantly with one or more of the following vaccines: live oral poliovirus vaccine (OPV), hepatitis B vaccine and *Haemophilus influenzae* type b vaccine (Hib).

In a small clinical trial in the United States *Infanrix* was given simultaneously, at separate sites, with hepatitis B vaccine, Hib and OPV at 2, 4 and 6 months of age. One month after the third dose of hepatitis B vaccine given simultaneously with *Infanrix*, 100% of infants demonstrated anti-HBs antibodies ≥10 mIU/mL (N=64). Ninety percent of infants who received Hib simultaneously with *Infanrix* achieved anti-PRP antibodies ≥1 mcg/mL (N=72), and 96% to 100% of infants who received OPV simultaneously with *Infanrix* showed protective neutralizing antibody to poliovirus types 1, 2 and 3 (N=60-61).

In the NIH Italian efficacy trial, 92% of infants received hepatitis B vaccine with the first and second dose of *Infanrix*. Ninety-four percent of infants received OPV with the first and second dose of *Infanrix*.

No data are available on the antibody response to measles, mumps and rubella vaccine (MMR), varicella vaccine or IPV when given concurrently with *Infanrix*.

VI. Advisory Panel Consideration

Data regarding the safety and efficacy of Infanrix were presented and discussed at the July 10, 1996 meeting of the FDA's Vaccines and Related Biological Products Advisory Committee meeting.

VII. Approved Package Insert

A copy of the approved package insert is attached.

Signatures.....

Theresa M. Finn, Chair

Julia Barrett

Van Sickler

Freyja Lynn

Juan Arciniega

Henry Hsu

Dale Horne

Alberto Gutiérrez

Kirsten Vadheim

Jane Halpern

Table 1. Adverse Events (AE) (%) Occurring Within the First Three Days Following Vaccination of Italian infants with Either *Infanrix* or Whole-Cell DTP at 2, 4 and 6 Months of Age

	Infanrix			Whole-Cell DTP vaccine		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
No. of infants	4,696	4,560	4,505	4,678	4,474	4,368
Local AE						
Redness	4.8	8.6	16.0	27.1	24.2	28.0
Redness ≥2.4 cm	1.0	1.3	3.5	12.4	7.3	7.7
Swelling	5.2	8.2	14.5	28.9	23.5	25.8
Swelling ≥2.4 cm	0.7	1.2	2.9	13.1	7.4	8.0
Tenderness	4.7	4.0	5.2	36.0	26.8	25.9
Systemic AE						
Fever ≥100.4°F*	7.1	7.9	9.0	46.8	36.1	39.8
Irritability	36.3	34.9	28.8	57.2	50.1	47.2
Drowsiness	34.9	18.8	11.4	54.0	34.1	23.0
Loss of Appetite	16.5	13.9	11.5	31.2	22.8	19.1
Vomiting	5.8†	4.1†	3.3	6.7	4.7	4.8
Crying ≥1 Hour	3.9	3.3	2.2	17.3	11.1	8.2

* Rectal temperatures.

† For the comparison of *Infanrix* and whole-cell DTP vaccine, all adverse events reached statistical significance at all doses except vomiting at doses 1 and 2 which was not statistically significant at $p<0.05$.

Table 2. Adverse Events (%) by the Third Evening After the First Three Doses of *Infanrix* or Whole-Cell DTP Administered to Infants

Vaccine	No. of doses	Redness	Swelling	Pain*	Fever (>101°F) †	Poor Appetite	Vomiting	Drowsiness	Fussiness ‡
Infanrix	1204	18.5	12.3	2.1	2.1	7.5	4.7	18.6	3.8
Whole-Cell DTP Lederle	220	36.8	25.5	14.1	9.1	18.6	5.0	36.4	15.5
Whole-Cell DTP Connaught	225	45.3	32.9	23.6	13.8	14.7	4.4	33.3	15.1

* Moderate or severe = cried or protested to touch or cried when leg moved.
† Rectal temperatures.
‡ Moderate or severe = prolonged crying and refusal to play or persistent crying that could not be comforted

Table 3. Adverse Events (AE) (%) Within 3 days of Vaccination with *Infanrix* in US Infants and Children in Which All Doses Were *Infanrix*

	Primary (N=120 infants)			Booster (N=76 children)
	Dose 1 (2 months)	Dose 2 (4 months)	Dose 3 (6 months)	Dose 4 (15 to 20 months)
Local AE				
Redness	16.6	15.4	26.3	39.5
Swelling	12.5	15.4	21.0	32.9
Pain*	5.0	5.1	0.9	10.5
Systemic AE				
Fever (>101°F)†	0.0	0.9	3.5	6.6
Anorexia	7.5	6.0	9.6	11.8
Vomiting	5.8	6.8	3.5	2.6
Drowsiness	37.5	19.7	13.2	6.6
Fussiness§	3.3	7.7	8.8	9.2

*Moderate or severe- cried or protested to touch or cried when limb moved.
†Rectal temperature for primary series; oral temperature for booster
§ Moderate or severe- prolonged crying and refusal to play or persistent crying that could not be comforted.

Table 4. Adverse Events (%) Within 3 Days of Vaccination with *Infanrix* in German Infants and Children in Which All Doses Were *Infanrix*

	Primary (N=2,457 infants)			Booster (N=1,809 children)*
Event	Dose 1 (3 months)	Dose 2 (4 months)	Dose 3 (5 months)	Dose 4 (10 to 36 months†)
Local				
Redness	8.9	23.6	26.6	45.9
Redness >2 cm	0.0	0.5	1.3	13.8
Swelling	3.9	14.1	18.5	35.4
Swelling >2 cm	0.0	0.3	1.3	11.4
Pain	2.0	2.6	3.7	26.3
Systemic				
Fever (≥100.4°F)§	6.3	8.3	13.3	26.4
Fever (>103.1°F)§	0.0	0.1	0.1	1.1
Loss of Appetite	8.0	7.4	6.5	11.6
Vomiting	4.3	3.9	3.4	2.9
Restlessness	10.3	9.5	8.6	15.9
Unusual Crying	3.9	4.3	4.1	6.4
Diarrhea	6.0	4.9	4.0	11.0

* may not be the same children as in the primary series

† mean = 20 months

§ Rectal temperatures.

Table 5. Comparison of Adverse Events (%) Within 3 Days of Vaccination with *Infanrix* or Whole-Cell DTP (Fourth Dose) in Children Who Had Received Three Previous Doses of the Same Vaccine

Event	*Infanrix* After *Infanrix* Primary (N=268)	Whole-Cell DTP After Whole-Cell DTP Vaccine Primary (N=92)
Local		
Redness	32.8	43.5
Redness >2 cm	4.5	3.3
Swelling	22.4	31.5
Swelling >2 cm	3.0	7.6
Pain*	15.7	55.4
Systemic		
Fever (≥100.4°F)†	26.9	64.1
Fever (>103.1°F)†§	0.4	4.3
Restlessness*	12.3	32.6
Loss of Appetite*	10.8	43.5
Vomiting	3.4	7.6
Drowsiness*	10.4	31.5
Unusual Crying*	7.8	33.7

* $p < 0.0001$.
† Rectal temperatures.
§ $p<0.05$

Table 6. Adverse Events (%) Occuring Within 3 Days Following Vaccination with *Infanrix* Administered at 15 to 20 Months and 4 to 6 Years of Age in Children Who Previously Received Three or Four Doses of Whole-Cell DTP

	15 to 20 months Three Previous Doses of Whole-Cell DTP		4 to 6 years Four Previous Doses of Whole-Cell DTP	
Event	*Infanrix* (N=110)	Whole-Cell DTP (N=55)	*Infanrix* (N=115)	Whole-Cell DTP (N=57)
Local				
Redness*	23	45	19	40
Redness† >10 mm	5	31	7	26
Swelling	14	24	15*	33*
Swelling >10 mm	7	15	8	18
Pain †§	5	38	12	40
Systemic				
Fever* ≥99.4°F‡	25	42	23	47
Fever† >100.5°F‡	2	20	1	12
Fussiness	34†	69†	20	30
Drowsiness	9*	24*	11	18
Poor Appetite*	9	20	6	16
Vomiting	2	0	1	4

* $p < 0.05$.
† $p < 0.0001$.
‡ Oral temperatures.
§ Moderate or severe = cried or protested to touch or cried when arm moved

Table 7. Severe Adverse Events Within 48 Hours of Vaccination with *Infanrix* or Whole-Cell DTP at 2, 4 or 6 Months of Age

	Infanrix (N=13,761 doses)		Whole-cell DTP (N=13,520 Doses)	
Event	**Number**	**Rate/1,000 Doses**	**Number**	**Rate/1,000 Doses**
Fever ≥104°F*†	5	0.36	32	2.4
Hypotonic-Hyporesponsive Episode‡	0	0	9	0.67
Persistent crying ≥3 hours*	6	0.44	54	4.0
Seizures	1§	0.07	3¶	0.22

* p <0.001.
† Rectal temperatures.
‡ p = 0.002.
§ Maximum rectal temperature within 72 hours of vaccination = 103.1°F.
¶ Maximum rectal temperature within 72 hours of vaccination = 99.5°F, 101.3°F and 102.2°F.