Date: October 31, 2003

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Subject: Clinical Review of New Product License Application for Tetanus and Diphtheria Toxoids Adsorbed For Adult Use, manufactured by Aventis Pasteur Limited

To: BLA STN# 103171

Through: Antonia Geber, M.D.
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Food and Drug Administration

cc: Jennifer Bridgewater
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2. GENERAL INFORMATION

Product Name: Tetanus and Diphtheria Toxoids Adsorbed For Adult Use

STN #:103171

Manufacturer: Aventis Pasteur Limited

Proposed Indications: Primary and booster immunization of persons seven years of age or older

Dosage Form: Liquid, single use vials and liquid, multidose (5 dose) vials

Adjuvant: Aluminum phosphate

Preservative: 2-phenoxyethanol

Route of Administration: Intramuscular

Product/Formulation (per 0.5 ml dose):
Tetanus toxoid 5 Lf
Diphtheria toxoid 2 Lf
Aluminum phosphate 1.5 mg (0.33 mg aluminum)
2-phenoxyethanol 3 mg
Formaldehyde ≤0.1 mg

Related Products Manufactured by Aventis Pasteur Limited:
- Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT) (STN #103944 approved April 1997)
- Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DAPTACEL) (PLA 96-0660, approved May 2002)
- ----------)
- Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine combined with Inactivated Poliovirus Vaccine used to reconstitute ActHIB (*Haemophilus influenza* Type b Conjugate Vaccine) [Pentacel--IND -------]

The manufacturing processes for both the tetanus and diphtheria toxoid components of the candidate Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td) are essentially identical to those used in the manufacture of Aventis Pasteur Limited's Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT) and for DAPTACEL, both of which are licensed in the U.S. These products have a higher amount of diphtheria toxoid than the candidate Td. The DT manufactured by Aventis Pasteur Limited contains thimerosal as a preservative; DAPTACEL contains 2-phenoxyethanol.

Administrative History:

A chronology of the review process is presented below.

- Original application (PLA #86-0205) submitted April 1986
- CBER non-approval letter March 1994
- Sponsor submission of complete response to CBER review June 2001

- CBER complete review letter #1 December 2001
- Sponsor submission of complete response to CBER review May 2002
- CBER complete review letter #2 November 2002
- Sponsor submission of complete response to CBER review May 2003

3. MATERIAL REVIEWED

- PLA# 86-0205 submitted April 1986
- BLA STN # 103171/0.5000 Volumes 1-6 submitted June 2001
- BLA STN # 103171/0.5002 Volumes 1 and 2 submitted October 2001
- BLA STN # 103171/0.5005 Volumes 1 and 2 attachments 1-38 and 40-54 submitted May 2002
- BLA STN # 103171/0.5008 Volume 1 submitted October 2002
- BLA STN # 103171/0.5011 Volume 1 submitted May 2003
- BLA STN # 103171/0.5016 submitted September 2003
- BLA STN # 103171/0.5019 submitted October 2003
- BLA STN # 103171/0.5020 submitted October 2003

4. CHEMISTRY/MANUFACTURING/CONTROLS (summary of key issues relevant to the clinical review)

4.1 Td vaccine used in primary immunization study: The Td vaccine used in the pivotal study of primary immunization contained thimerosal rather than 2-phenoxyethanol as a preservative. In addition, since the lots of Td used in the primary immunization study were formulated, there have been some changes in the manufacturing methods. Most notably, there has been ----------for *C. tetani* and *C. diphtheriae*, and a change in the purification of tetanus toxoid from a ----------. The implications of these product and manufacturing differences on the generalizability of the results of the primary immunization study to the current candidate Td have been discussed internally within CBER. Consideration was also given to the fact that it may not be feasible to conduct another primary immunization study because of the difficulty in identifying a naive population with regard to tetanus and diphtheria immunity. CBER decided that despite the manufacturing and product differences for the Td vaccine used in the primary immunization study, the data from the study should be sufficiently generalizable to the currently manufactured Td. The results of the primary immunization study will be discussed in detail in a subsequent section.

4.2 Manufacturing consistency of Td

For reasons that will be detailed in a subsequent section of this memo, the clinical data submitted to the BLA to support lot consistency of the candidate Td vaccine are insufficient. Based on internal discussions within CBER, it was decided that data on lot consistency of the ----------, could be used to support lot consistency of the candidate Td vaccine. ----------.

4.3 Tetanus ELISA

In the pivotal studies of booster immunization with the candidate Td vaccine, antibodies to tetanus toxin were measured using an ELISA. Information on the ELISA methods and assay validation were reported to be acceptable by the product reviewer assigned to the BLA committee. In addition, the product reviewer reported that data submitted to the BLA support a good correlation between the ELISA used in these studies and an in vivo serum toxin neutralization test, across the range of the assay. In the tetanus ELISA used in the pivotal studies on booster immunization, an internal reference antitoxin was used

rather than the World Health Organization international standard antitoxin. ELISA results were then converted from ELISA units to International units, using a conversion factor derived from an analysis that compared the strength of the internal standard relative to the international standard (Lot ------). The data for this analysis were obtained from tetanus ELISA testing conducted over approximately a one-year period that included a total of 592 plates. The analyses to determine the conversion factor for ELISA units to International units were reviewed by the product reviewers for the BLA.

4.4 Other assays

Other assays used in clinical trials submitted to the BLA included the serum tetanus toxin ---------- (primary immunization study, historical Td lot consistency study, historical Td-IPV study), in vitro---------- for diphtheria (primary immunization study, pivotal booster immunization studies, historical Td-IPV study), the ---------- neutralization test for diphtheria antitoxin (historical Td lot consistency study). No particular concerns regarding these assays were raised by the product reviewer.

5. GENERAL CLINICAL BACKGROUND

5.1 Foreign experience: Td consisting of 5 Lf of tetanus toxoid and 1-2 Lf of diphtheria toxoid, manufactured by Aventis Pasteur Limited, is licensed in five countries (Canada, Germany, Columbia, Dominican Republic, and Mexico). During a seven year period from July 1993-July 2000, >17 million doses of the sponsor's Td vaccine have been distributed worldwide. The widest experience with this vaccine has been in Canada. Td manufactured by Aventis Pasteur Limited that is currently marketed in Canada differs in formulation from the vaccine intended for the U.S. market in terms of the preservative (thimerosal in the Td marketed in Canada vs. 2-phenoxyethanol in the Td intended for U.S. use).

With the exception of the province of Quebec, Aventis Pasteur Limited has always been the sole supplier of diphtheria toxoid for Canada. In the mid-1980's, following the introduction of alum adsorbed vaccines in the rest of Canada, Quebec converted to the diphtheria toxoid produced by Aventis Pasteur Limited. With the exception of the province of Quebec, since the mid-1980s, Aventis Pasteur Limited has been the sole supplier of tetanus toxoid-containing vaccines for persons 7 years of age and older in Canada. In the mid-1980's, Quebec converted to the tetanus toxoid produced by Aventis Pasteur Limited, except for a few years in the mid-1990s when a Td vaccine from a different manufacturer was also distributed.

Summary of Diphtheria Epidemiology in Canada *(based on information submitted to the Td BLA)**:*** Following the introduction of diphtheria toxoid in Canada in 1926, and its widespread use in infants and children beginning in 1930, the number of reported cases of diphtheria declined from 9,000 cases in 1924 to an average of 2,000 cases annually in the immediate post-vaccination period, followed by more dramatic declines by the mid-1950s. The downward trend continued until 1964, when only 23 cases (an incidence rate of 0.1 per 100,000) were reported. Active laboratory surveillance, with the inclusion of carriers, contributed to an increase in annual incidence in 1974 (0.8 per 100,000). Since the late 1970s, the incidence rate of diphtheria has ranged from 0 to 0.5 per 100,000 population. However, the steep decline in incidence starting from 1980 has been attributed, in part, to a change in case definition in 1980 to exclude carriers from reported cases. Two to five cases were reported annually between 1986 and 1995. During the years 1996-2001, a total of three cases were reported (one each in 1997, 1999, and 2001). The age distribution of 30 cases reported during the 12-year period 1986-1997 for whom age information is available shows that 50% occurred among persons ≥30 years, 23% among those aged 5 to 9 years, and 13% each in the 10- to 19- year old and 20- to 29-year old age groups. Specific information was not provided on the vaccination status of reported cases.

It should be noted that most recent epidemiologic data are based on the case definition for national notification of diphtheria in Canada developed in 1991, which was as follows: "Clinically compatible symptoms involving upper respiratory tract (pharyngitis or laryngitis) with or without a membrane and/or toxin (cardiac or neurologic) symptoms in a person from whom toxigenic *C. diphtheriae* has been isolated." As of 1998, there was no uniform reporting of mild respiratory cases or cutaneous cases of

diphtheria. Data are not available on the current actual level of circulation of toxigenic *C. diphtheriae* in Canada.

National estimates of immunization coverage against diphtheria in 1997 indicate that 98% of children have received at least three doses of a diphtheria toxoid containing vaccine by the second birthday and 84% have received the recommended primary series of four doses. Available data suggest a lower uptake of diphtheria booster immunization among adults—probably no higher than 60%, and likely much lower.

Summary of Tetanus Epidemiology in Canada *(based on information submitted to the Td BLA)**:*** During the 1920s and 1930s, 40 to 50 deaths from tetanus were reported annually. Mortality due to tetanus declined rapidly after the introduction of tetanus toxoid in 1940. Five deaths from tetanus have been reported between 1980 and 1991, with none since 1991. From 1989 through 1998, two to seven cases of tetanus were reported annually, with no more than two cases reported annually from 1999-2001. Of 11 published reports of tetanus cases since 1991, vaccination history was provided in seven. One case occurred in a person who was reported to have received a full primary series, as well as a recent booster dose within 28 months prior to injury. The vaccine manufacturer was not stated. The other cases had either not received a complete primary series, or the most recent booster dose was at least 15 years prior to the injury.

5.2 Assessment of human immunogenicity to tetanus and diphtheria toxoids:

Tetanus: Protection against disease is due to the development of neutralizing antibodies to the tetanus toxin. The gold standard for measuring an immune response to tetanus toxoid is the serum toxin neutralization test. Such tests are performed in mice injected with mixtures of various dilutions of serum and a lethal dose of tetanus toxin, and standardized to a reference serum specimen. Other serological tests, such as ELISA, are useful provided that correlation with toxin neutralization has been demonstrated. A serum tetanus antitoxin level of 0.01 IU/ml historically has been considered the minimum level needed to ensure protection.[1, 2] More recently, a level $\geq$0.1 to 0.2 IU/ml has been considered as protective.[3]

Diphtheria: The in vivo neutralization test is the gold standard for measuring an immune response to diphtheria toxoid. This test is based on injecting serial dilutions of serum mixed with fixed amounts of toxin into the depilated skin of rabbits or guinea pigs, and estimating the antitoxin concentration from the inflammatory reaction. An in vitro neutralization test ----------has shown good correlation with the in vivo neutralization test. Available data indicate that in most circumstances, an antitoxin level of 0.01 IU/ml is the lowest giving some degree of protection, while levels $\geq$0.1 IU/ml may be needed for full protection.[4] Levels of 1.0 IU/ml and above are thought by some to confer long-term protection.[4] Additional factors may influence a person's susceptibility to infection, including the dose and virulence of the bacteria, and the individual's general immune status. The proportion of immune persons necessary to confer diphtheria herd immunity has been estimated at 70% to 80%.

5.3 Recommendations for routine administration of Td in the U.S.

The Advisory Committee on Immunization Practices (ACIP) recommends booster immunization with Td at 11-12 years of age if at least 5 years have elapsed since the last dose of vaccine containing diphtheria and tetanus toxoids. Subsequent routine Td boosters are recommended every 10 years.[3]

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[1] Wassilak SGF, Orenstein WA, and Sutter RW. Tetanus Toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines.* 3rd ed. Philadelphia, PA: W.B. Saunders Company; 1999:441-474.

[2] Department of Health and Human Services, Food and Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review; Proposed rule. *Federal Register* December 13, 1985;50(240):51002-51117.

[3] Centers for Disease Control and Prevention. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR* 2002;51(RR-2):1-35

[4] Mortimer EA and Wharton M. Diphtheria Toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines.* 3rd ed. Philadelphia, PA: W.B. Saunders Company; 1999:140-157

5.4 Recent shortage of tetanus and diphtheria toxoids in the U.S.

From the last quarter of 2000 through the second quarter of 2002, a shortage of Td vaccine and tetanus toxoid existed in the United States. The shortage resulted from decreased production in 2000 by both U.S. manufacturers (Wyeth Lederle [Pearl River, New York] and Aventis Pasteur [Swiftwater, Pennsylvania]), and the decision by Wyeth Lederle to cease Td production in 2001. The amount of Td distributed nationally decreased 40% during 2001-2002, compared with pre-shortage distribution levels. To assure vaccine availability for priority indications, the ACIP recommended delaying all routine Td boosters in adolescents and adults during the period May 2001-June 2002. In June 2002, the supply of Td in the U.S. became sufficient to permit resumption of the routine schedule for Td use as recommended by the ACIP.[5]

6. GENERAL DESCRIPTION OF CLINICAL DATA SOURCES

This BLA contains clinical safety and immunogenicity data from three "historical" studies that were originally submitted in 1986, as well as from four more recent clinical studies, which have been conducted as part of the sponsor's Clinical Development Programs for TdcP and TdcP combined with inactivated poliovirus vaccine (TdcP-IPV). With the exception of one historical primary immunization study in 18 subjects ages 6-56 years, all other studies examined the use of Td and/or Td combination(s) as a booster immunization. Of the six booster immunization studies, three studies (one historical and two recent) included a Td vaccine group. Booster immunization studies are summarized in Table 1 below.

Table 1. Summary of clinical trials that examined booster immunization with Td and/or Td combination vaccines

Historical Studies	Age (yrs)	Td	Td-IPV[1]	TdcP	TdcP-IPV[1]	Total
Canadian Armed Forces	17-29	347				347
Td-IPV Study	14-17 18-19		256 20			256 20
Subtotal	**14-29**	**347**	**276**	**0**	**0**	**623**
Recent Studies	Age	Td	Td-mIPV[2]	TdcP	TdcP-IPV[1]	Total
TC9704	12-17 18-54	37 263		55 394		92 657
TD9707	12-18 19-65[3]	-- 126	117 --	-- 244	351 369	468 739
TD9805	11-14	--	--	269	--	269
TD9809	11-14	--	--	--	277	277
Subtotal	**11-65**	**426**	**117**	**962**	**997**	**2,502**
TOTAL	**11-65**	**773**	**393**	**962**	**997**	**3,125**

[1] Vero cell derived IPV
[2] MRC-5 cell derived IPV
[3] According to the study protocol, the eligible age range was 12-59 years; apparently, some subjects 60-65 years of age were enrolled in the TdcP-IPV group.
Source: STN:103171/0.5000, Volume 1, page 9

Table 2 summarizes the number of subjects, by age group, who received a booster dose of Td or a Td combination vaccine in historical and recent studies.

[5] CDC. Resumption of routine schedule for tetanus and diphtheria toxoids. MMWR 2002;51:529-530.

Table 2. Summary of subjects who received a booster dose of Td or Td combination vaccines[1] in historical and recent studies

	Age group[3]	**Td**	Td combination[2]
Historical	adolescents		256
	adults[4]	347	20
Recent	adolescents	37	1069
	Adults	389	1007
Total	**adolescents**	**37**	1325
	Adults	**736**	1027

[1] Subjects received Td in one historical study (Canadian Armed Forces) and two recent studies (TD9704 and TD9707); subjects received Td combinations in one historical study and four recent studies (TD9704, TD9707, TD9805, and TD9809).
[2] Td combinations evaluated are TdcP, Td-IPV, TdcP-IPV
[3] Age groupings, by year of age, differed between studies. Therefore, in the table there is some overlap, by year of age, in the adolescent and adult groups. Overall, subjects categorized as adolescents ranged in age from 11-18 years, and subjects categorized as adults ranged in age from 17-65 years of age. Each subject is counted only once in the Table.
[4] Subjects ranged in age from 17-29 years, with 48.4% of subjects ages 17-19 years, and 51.3% ages 20-29 years.
Source: STN:103171/0.5000, Volume 1, page 9

Overall, the quality, reliability, and reproducibility of the data from the historical studies are difficult to assess, due, in part, to limited information on study methods. A limitation of the recent clinical studies is that none were designed to specifically evaluate the candidate Td vaccine. Rather, these studies were primarily conducted to examine the safety and immunogenicity of Td combined with other antigens. Only two of the recent clinical studies included a Td study group. Immunogenicity data on Td combined with other antigens must be interpreted in view of the possibility that other antigens may affect the immunologic response to Td. Other antigens may also affect the adverse event profile of Td. Thus, the most relevant and critical data for evaluating the safety and immunogenicity of the candidate Td vaccine are from the Td study groups of two recent studies.

Finally, a limitation of the studies submitted in this BLA is that none included a control group of subjects who received a U.S. licensed Td vaccine. There are few available historical data from prospective clinical trials of Td vaccines that have been licensed in the U.S. to provide a reference for interpretation of safety and immunogenicity data on the candidate Td vaccine.

The subsequent three sections of this review provide a more detailed description of the clinical studies. These sections are organized as follows:
Section 7. Td for Primary Immunization: Historical study on primary immunization.
Section 8. Pivotal Clinical Data on Booster Immunization: Data on Td study groups from two recent studies (TC9704 and TD9707).
Section 9. Supplemental Clinical Data on Booster Immunization:
- Data on study groups that received Td combined with other antigens in recent studies
- Data on Td and Td combinations from historical studies

7. PRIMARY IMMUNIZATION: Efficacy Study of Tetanus and Diphtheria Toxoids Adsorbed For Adult Use For Primary Immunization

7.1 Study Period: Not specified; original study report dated 1983.

7.2 Objective: Document the efficacy and acceptability of Td for primary immunization

7.3 Design/Population: Previously unimmunized persons (N=18) ages 6 years of age and older received three intramuscular injections of Td, according to the schedule described below. The study was conducted in Canada.

Vaccine Contents: Each 0.5 ml dose of Td contained 5 Lf of tetanus toxoid, 2 Lf of diphtheria toxoid, 1.5 mg aluminum phosphate, with thimerosal 0.01% added as a preservative.

Vaccine Lots: Vaccine lots in general distribution were used. Three lots (1001-21, 1002-11 and 1004-12) were used for the first dose. Subsequent doses were with these three lots or with lot 1003-12. For each subject, different lots may have been used for the three doses of the Td series.

7.4 Protocol

Vaccination schedule: The first two doses of Td were separated by an interval of two months, followed by a third injection of Td six to eight months later.

Endpoints: Diphtheria and tetanus antitoxin levels. Criteria for demonstrating efficacy of primary immunization with Td were not specified.

Efficacy evaluation: Blood samples were obtained prior to, and seven days following the first dose, and at four weeks following the second and third doses. Tetanus antitoxin levels were determined by the mouse toxin neutralization test, and diphtheria antitoxin levels were determined by the micro neutralization test using tissue culture.

Safety evaluation: Subjects were monitored for three days following each vaccination for local and general reactivity associated with the vaccine.

7.5 Results:

7.5.1 Population. Eighteen subjects were enrolled. Eight subjects were 6-9 years of age and 10 subjects were 17-56 years of age. Two-thirds were female. Information on race and ethnicity of study participants was not collected.

7.5.2 Efficacy

Immunogenicity-- tetanus: For all subjects, tetanus antitoxin level pre-vaccination and 7 days post-vaccination was <0.01 IU/ml, consistent with no history of previous immunization against tetanus. Seventeen of 18 subjects had available tetanus antitoxin levels four weeks following the second and third doses of Td. Following each of these doses, all 17 subjects had a tetanus antitoxin level >0.1 IU/ml. Sixteen subjects achieved a level >1.0 IU ml after the third dose. The subject who did not have a tetanus antitoxin level following the second dose had a level of 14.0 IU/ml following the third dose.

Immunogenicity-- diphtheria: For all subjects, diphtheria antitoxin level pre-vaccination and 7 days post-vaccination was <0.01 IU/ml, consistent with no history of previous immunization against diphtheria. Of 17 subjects who had an available diphtheria antitoxin level four weeks following the second dose of Td, all had a level $\geq$0.01 IU/ml, including seven whose levels were >0.1 IU/ml. Of 17 subjects who had an available diphtheria antitoxin level four weeks following the third dose of Td, all achieved a level >0.1 IU/ml. The subject who had no diphtheria antitoxin level available following the second dose had a level of 5.12 IU/ml following the third dose. The subject who had no diphtheria antitoxin level available following the third dose had a level of 0.04 IU/ml after the second dose.

7.5.3 Safety The sponsor reported that "none of the individuals experienced clinical reactivity of significance associated with the injections of the vaccine. Occasional individuals reported redness at the injection site and some localized itchiness following the third vaccine injection." Information on frequencies of specified adverse events was not provided.

7.6 Reviewer's Comments and Conclusions on Td Primary Immunization Study

A proposed rule published in the Federal Register in 1985 included recommendations of the Panel on Review of Bacterial Vaccines and Toxoids (the Panel) for demonstrating efficacy of primary immunization with tetanus and diphtheria toxoids.[2] For tetanus toxoid, the Panel defined an acceptable level of immunity as over 80% of previously non-immune subjects having $\geq$0.01 IU/ml of tetanus antitoxin in a serum sample drawn 10-14 days after two doses of adsorbed tetanus toxoid, or over 80% having $\geq$0.1 IU/ml in a serum sample drawn 10-14 days after a third dose (administered 6-12 months after the second dose). The Panel noted that the 80% "success" by either criterion is a minimum tolerated level, and that the success rate in many previously reported studies was 95-100%. For diphtheria toxoid, the Panel defined serologic immunity as 80% conversion of seronegative subjects to seropositivity (defined as a serum level of diphtheria antitoxin $\geq$0.01 units/ml) by one month after a second dose of adsorbed diphtheria toxoid (administered 4 weeks after the first dose). A sample protocol for studying the efficacy of primary immunization with tetanus toxoid indicated that a study of 20 subjects, with 19 achieving an acceptable level of immunity, as defined above, would constitute adequate documentation of efficacy, on a 95% probability basis. If fewer than 19 subjects achieved an acceptable level of immunity, then a second sample of 20 subjects should be examined. Of 40 subjects, 36 would need to achieve an acceptable level of immunity.

The results of the primary immunization study do not fully meet the minimum sample size criteria (at least 19 seroconverters in a sample of 20 subjects) set forth by the Panel, as described above. However, among 17 subjects, all achieved levels of immunity to both tetanus and diphtheria toxins considered acceptable by the Panel. A previous statistical review at CBER indicated that from this study, one can conclude, with 95% probability, that the seroconversion rate for the Td vaccine is at least 80%, the threshold of acceptability set by the Panel. There were minor differences in the vaccination schedule and timing of serum sampling in the sponsor's study compared to that outlined by the Panel. In the vaccination schedule referred to by the Panel, the interval between the first two doses was four weeks, compared to two months in the sponsor's study. In the Panel's sample protocol for assessing efficacy of tetanus toxoid, serum samples would be obtained 10-14 days after the second or third dose, whereas in the sponsor's study, sera were obtained four weeks after each dose. In my opinion, the differences in vaccination schedule and serum sampling are likely to have little clinical relevance in the overall assessment of the efficacy of primary immunization with the candidate Td vaccine.

The Td vaccine used in this historical study contained the same amount of tetanus and diphtheria toxoids as the currently manufactured vaccine. However, it contained thimerosal rather than 2-phenoxyethanol as a preservative. In addition, since the lots of Td used in this study were formulated, there have been some changes in the manufacturing methods. Most notably, there has been ---------- for *C. tetani* and *C. diphtheriae*, and a change in the purification of tetanus toxoid from a ----------. The implications of these product and manufacturing differences on the generalizability of the results to the current candidate Td have been discussed internally within CBER. Consideration was given to the fact that it may not be feasible to conduct another primary immunization study because of the difficulty in identifying a naive population with regard to tetanus and diphtheria immunity. CBER decided that the historical data on primary immunization are sufficient for approval of a primary immunization indication for the candidate Td.

8. PIVOTAL CLINICAL DATA ON BOOSTER IMMUNIZATION

8.1 TdcP Study TC9704: Safety and Immunogenicity of One Lot of Td Combined with Three Lots of Component Pertussis (TdcP) Vaccine Compared to Td and cP Given Separately in Adults and Adolescents

8.1.1 Study Period: July 1997-January 1998

8.1.2 Objective: To compare the safety and immunogenicity of three lots of TdcP with one lot of Td and one lot of cP (administered separately one month apart) in adolescents and adults 12-54 years of age.

8.1.3 Design: Phase II, randomized, multi-center (4 sites) double blind, five-armed controlled clinical trial using three lots of TdcP, one lot of Td, and one lot of cP. For Groups 1 and 2, trial personnel and participants were blinded as to which vaccine was being administered.

Table 3. Study TC9704 Study Groups

Group	Vaccine(s)
1*	Td → cP
2*	cP → Td
3	TdcP-1
4	TdcP-2
5	TdcP-3

*Groups 1 and 2 received Td and cP 28-35 days apart

Table 4. Study TC9704 Vaccines and lot numbers

Vaccine	Lot Number
Td	001-11
cP	1001-11
TdcP-1[1]	21-11
TdcP-2[1]	22-11
TdcP-3[1]	23-11

[1] Diphtheria Concentrate DCA-018 and Tetanus Concentrate TCA-012 were used to formulate all three TdcP lots.
Source: STN:103171/0.5000, Volume 1, page 77; Volume 9, pages 72, 89, and 106

Table 5. Study TC9704 Vaccine contents per 0.5 ml dose

Components	Td	cP	TdcP
Tetanus toxoid	5 Lf		5 Lf
Diphtheria toxoid	2 Lf		2 Lf
Pertussis toxoid		2.5 µg	2.5 µg
Filamentous hemagglutinin (FHA)		5 µg	5 µg
Fimbriae 2+3		5 µg	5 µg
Pertactin		3 µg	3 µg
Aluminum phosphate	1.5 mg	1.5 mg	1.5 mg
2-phenoxyethanol	0.6%	0.6%	0.6%

Source: STN:103171/0.5000, Volume 1, page 77

8.1.4 Protocol

Population: The study was conducted at four study centers in Canada.

Inclusion criteria

- age ≥12 years and <55 years

- informed consent obtained
- good health on basis of medical history
- able to cooperate with requirements of the study
- for females, use of an effective method of contraception during study and negative pregnancy test prior to vaccination OR post menopausal, OR only sexual partner sterilized (if male)

Exclusion criteria

- Pregnancy or planning a pregnancy during study period
- Known or suspected primary disease of the immune system
- Malignancy or receiving immunosuppressive therapy
- Receipt of any pertussis, diphtheria, or tetanus containing vaccines within previous 5 years
- any significant underlying chronic disease
- known impairment of neurologic function or seizure disorder
- personal history of physician diagnosed or laboratory confirmed pertussis within the last 2 years
- receipt of blood products or immunoglobulin within the previous 3 months
- known or suspected allergy to any of the vaccines intended for use in the study
- receipt of any vaccine within 2 weeks of receiving a study vaccine
- daily use of non-steroidal anti-inflammatory drugs

Reasons for deferring vaccination

- febrile illness within previous 72 hours; immunization deferred at least 48 hours.

Contraindications for second immunization

- anaphylactic reaction within 48 hours following immunization

Vaccination schedule: TdcP recipients received a single dose of vaccine. Subjects in Groups 1 and 2 received Td and cP vaccines 28-35 days apart. Vaccines were injected intramuscularly into the deltoid.

Concomitant Vaccines: Neither specified nor prohibited.

Endpoints relevant to the evaluation of Td *(note: the study was designed primarily to evaluate the safety and immunogenicity of TdcP relative to Td or cP)*

- Proportion of subjects reporting specified local and general adverse events within 15 minutes of vaccination, at 22-26 hours, 70-74 hours, and 8-10 days post-vaccination
- Proportion of subjects with post-immunization levels of antibodies to tetanus and diphtheria toxins $\geq$0.01 IU/ml, $\geq$0.1 IU/ml, and $\geq$1.0 IU/ml, 95% confidence intervals
- Pre- and post-vaccination geometric mean antibody titers (GMTs) to tetanus and diphtheria toxins, and 95% confidence intervals
- Ratio of pre- and post-vaccination GMTs to tetanus and diphtheria toxins, and 95% confidence intervals
- Proportion of subjects achieving 4-, 10-, and 20-fold increases in antibody titer to tetanus and diphtheria toxins, and 95% confidence intervals

Surveillance:

Safety: Subjects were monitored for 15 minutes immediately following immunization and for one month post-immunization. Specified local adverse events (redness, swelling, and tenderness) and systemic symptoms (fever, altered appetite, headaches, general malaise, chills, decreased energy, sore or swollen joints, nausea, vomiting, diarrhea, and muscle aches) were monitored for 10 days following vaccination. Diary cards were not used. Study sites were provided with a subject worksheet to use as a template for their source documents. Some sites used the provided template or a modified template for this purpose, and some sites distributed the provided template or a modified template to subjects to assist in recording adverse events. Subjects were provided with templates for measuring sizes of local redness or swelling, and with digital thermometers for measuring oral temperature. At three points post-vaccination—22-26 hours, 70-74 hours, and 8-10 days, study personnel administered a questionnaire to subjects, via telephone, to assess local and systemic reactions. Information on adverse events occurring after 8-10 days was collected at the subsequent visit, approximately one month post-immunization. Information on

intercurrent illness and consultation with a physician was collected throughout the study (i.e., from receipt of the first dose to 28-35 days post 1st or 2nd dose.

Adverse events were either measured (i.e., redness, swelling, and fever) or graded for severity using the following criteria: mild (noticeable, but did not interfere with activities); moderate (interfered with activities, but did not require medical care or absenteeism); severe (incapacitating, unable to perform usual activities, required medical care or absenteeism).

Subjects were asked to notify the study nurse immediately if any serious adverse event occurred during the study period. A serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening, resulted in persistent or significant disability/incapacity, required inpatient hospitalization, prolonged existing inpatient hospitalization, or resulted in a congenital anomaly/birth defect. Medical and scientific judgment was to be used to decide whether other events not meeting these criteria were also serious.

Efficacy (Immunogenicity): A blood sample was obtained from each subject prior to immunization at visit 1. Subjects in Groups 1 and 2 had blood drawn prior to their second immunization at visit 2, and 28-35 days after the second immunization. Subjects in the TdcP groups (groups 3, 4, and 5), had blood drawn 28-35 days after immunization. Sera were tested for antibodies to tetanus toxin using an ELISA and for antibodies to diphtheria toxin using a ---------- assay (---------- method), as well as for antibodies to pertussis antigens. Assays were performed by ----------

Statistical plan: The statistical plan and sample size determination were based on the primary objective of comparing TdcP to the Td or cP control groups. It was assumed that at least 95% of subjects in the Td group would achieve post-vaccination antibody levels ≥0.1 IU/ml for diphtheria and ≥0.1 IU/ml for tetanus, based on the historical study of Td conducted in Canadian Armed Forces recruits who ranged in age from 17-29 years. Using these levels to define seroprotection, the sample size provided >90% power to detect a 10% difference in seroprotection rates between individual TdcP groups vs. the Td group, or a 5% difference for the combined TdcP lots vs. Td.

8.1.5 Results

8.1.5.1 Population (all study groups): A total of 755 subjects were enrolled and immunized, with approximately 150 subjects per each of the five study groups. Six subjects were withdrawn after immunization for the following reasons: desired pregnancy; lost to follow-up; unspecified; didn't want 2nd immunization; received dose of vaccine not required due to mislabeled vial; and adverse event (described below in section on Safety Results). During the study, nine subjects received non-study vaccines, none of which were administered on the same day as study vaccine.

Table 6. Study TC9704 Characteristics of study population (all study groups)

Characteristic	
Gender	
Male n (%)	240 (32)
Female n (%)	509 (68)
Age	
Mean (years)	33.7
Range (years)	12.0-54.7
Adolescents ages 12-17 years[1] n (%)	92 (12.3)
Adults ages 18-54 years[2] n (%)	657 (87.7)

[1] 37 adolescents were in Study Groups 1 or 2 and received Td
[2] 263 adults were in Study Groups 1 or 2 and received Td

Source: STN:103171/0.5000, Volume 1, page 107

Among 263 adults who received Td, 75 (28.5%) were male and 188 (71.5%) were female. Among 37 adolescents who received Td, 20 (54.1%) were male and 17 (45.9%) were female.

Information on race and ethnicity of study participants was not collected.

8.1.5.2 Immunogenicity data for subjects who received Td: See Tables 7-13.

Table 7. Study TC9704 Tetanus GMTs (IU/ml) pre- and one month post-immunization with Td, by age group

	Pre			Post		
	n	GMT	(95% CI)	n	GMT	(95% CI)
Adults	263	1.07	(0.92, 1.25)	263	13.61	(12.13, 15.26)
Adolescents	37	0.35	(0.23, 0.55)	37	19.68	(14.40, 26.91)

[1] ages 18-54 years
[2]ages 12-17 years
Source: STN:103171/0.5020, page 1

Table 8. Study TC9704 Proportion of subjects with specified levels of tetanus antibody, pre- and 1-month post-immunization, adolescents and adults who received Td

			≥ 0.01 IU/ml			≥ 0.1 IU/ml			≥ 1.0 IU/ml		
Group	Timing	N	n	%	(95 % CI)	n	%	(95 % CI)	n	%	(95 % CI)
Adults[1]	pre	263	260	98.9	(96.7, 99.8)	250	95.1	(91.7, 97.3)	143	54.4	(48.1, 60.5)
	post	263	263	100.0	(98.6, 100.0)	262	99.6	(97.9, 100.0)	260	98.9	(96.7, 99.8)
Adolescents[2]	pre	37	36	97.3	(85.8, 99.9)	33	89.2	(74.6, 97.0)	4	10.8	(3.0, 25.4)
	post	37	37	100.0	(90.5, 100.0)	37	100.0	(90.5, 100.0)	37	100.0	(90.5, 100.0)

[1] ages 18-54 years
[2]ages 12-17 years
Source: STN:103171/0.5020, page 2

Table 9. Study TC9704 Proportion of subjects with a booster response[1] to tetanus toxoid following Td, by age group

Group	N	n	%	(95% CI)
Adults[2]	263	212	80.61	(75.3, 85.2)
Adolescents[3]	37	37	100.0	(90.5, 100.0)

[1] Booster response is defined as a ≥4-fold increase in post-vaccination anti-toxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 IU/ml must also have a post-vaccination level ≥0.1 IU/ml to be considered a responder.
[2] ages 18-54 years
[3]ages 12-17 years
Source: STN:103171/0.5020, page 3

The proportion of adult subjects who demonstrated a booster response to tetanus toxoid following vaccination with Td was 74.7% for males and 83% for females.

Table 10. Study TC9704 Diphtheria GMTs (IU/ml) pre- and one month post-immunization with Td, by age group

	Pre		Post	
	n	GMT (95% CI)	n	GMT (95% CI)
Adults[1]	263	0.05 (0.04, 0.06)	263	0.86 (0.68, 1.10)
Adolescents[2]	37	0.12 (0.06, 0.21)	37	9.87 (5.15, 18.93)

[1]ages 18-54 years
[2]ages 12-17 years
Source: STN:103171/0.5005, Volume 1, page 184

Table 11. Study TC9704 Proportion of subjects with specified levels of diphtheria antibody, pre- and 1-month post-immunization, adolescents and adults[1] who received Td

			≥ 0.01 IU/ml			≥ 0.1 IU/ml			≥ 1.0 IU/ml		
Group	Timing	N	n	%	(95 % CI)	n	%	(95 % CI)	n	%	(95 % CI)
Adults[1]	pre	263	207	78.7	(73.3, 83.5)	101	38.4	(32.5, 44.6)	11	4.2	(2.1, 7.4)
	post	263	260	98.9	(96.7, 99.8)	223	84.8	(79.9, 88.9)	146	55.5	(49.3, 61.6)
Ado-	pre	37	33	89.2	(74.6, 97.0)	21	56.8	(39.5, 72.9)	4	10.8	(3.0, 25.4)
lescents[2]	post	37	37	100	(90.5, 100)	37	100	(90.5, 100)	31	83.8	(68.0, 93.8)

[1]ages 18-54 years
[2]ages 12-17 years
Source: STN:103171/0.5005, Volume 1, page 187

Table 12. Study TC9704 Proportion of subjects with specified levels of diphtheria antitoxin following vaccination with Td, by pre-vaccination diphtheria antitoxin level and age group, subjects with pre-vaccination level <0.1 IU/ml

			Post-vaccination diphtheria antitoxin level (IU/ml)					
			≥ 0.01			≥ 0.1		
Group	pre-vaccination level (IU/ml)	N	n	%	(95 % CI)	n	%	(95 % CI)
Adults[1]	<0.01	56	53	94.6	(85.1, 98.9)	24	42.9	(29.7, 56.8)
	0.01-<0.1	106	106	100	(96.6, 100)	98	92.5	(85.7, 96.7)
Adolescents[2]	<0.01	4	4	100	(39.8, 100)	4	100	(39.8, 100)
	0.01-<0.1	12	12	100	(73.5, 100)	12	100	(73.5, 100)

[1]ages 18-54 years
[2]ages 12-17 years
Source: STN:103171/0.5005, Volume 1, page 189

Among adults who received Td, the same proportion of males and females, 21%, had pre-vaccination diphtheria antitoxin levels <0.01 IU/ml. Of these subjects, 37.5% of males and 45.0% of females had post-vaccination diphtheria antitoxin levels ≥0.1 IU/ml. Among adults with pre-vaccination diphtheria antitoxin levels between 0.01-<0.1 IU/ml, 86.2% of males and 94.8% of females had a post-vaccination diphtheria antitoxin levels ≥0.1 IU/ml.

Table 13. Study TC9704 Proportion of subjects with a booster response[1] to diphtheria toxoid following vaccination with Td, by age group

Group	N	n % (95 % CI)
Adults[2]	263	204 77.6 (72.0, 82.5)
Adolescents[3]	37	37 100 (90.5, 100)

[1] Booster response is defined as a ≥4-fold increase in post-vaccination anti-toxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 IU/ml must also have a post-vaccination level ≥0.1 IU/ml to be considered a responder.
[2]ages 18-54 years
[3]ages 12-17 years
Source: STN:103171/0.5005, Volume 1, page 192

The proportion of adult subjects who demonstrated a booster response to diphtheria toxoid following vaccination with Td was 72.0% for males and 79.8% for females.

8.1.5.3 Safety data for subjects who received Td. Information on adverse events was collected at protocol specified intervals after each immunization. All data were analyzed, regardless of whether the contacts were made within the specified windows. For the 22-26 hour and 70-74 hour post-vaccination intervals, 90-97% of contacts occurred within the specified window. For the 8-10 day post-vaccination interval, approximately 63% of contacts occurred within the specified window.

Frequencies of solicited local adverse events and selected systemic adverse events reported during the first 72 hours following Td vaccination are presented by age group in Table 13. Although not shown in the table, in both adults and adolescents, there was a tendency towards a higher frequency of local pain and swelling among females compared with males, although comparative statistical analyses, by gender, were not performed. The magnitude of the gender differences in the reported frequencies of local adverse events was greatest for pain. For example, among adolescents and adults, combined, 90.7% of females reported pain within 72 hours following vaccination compared with 70.5% of males. This trend was also observed in subjects who received TdcP. Overall, the frequency of local adverse events was highest during the first 24 hours post-vaccination, and declined during the subsequent observation periods (24-72 hours post-vaccination, and 72 hours - 10 days post-vaccination). During the period 72 hours - 10 days post-vaccination, 13.3% of subjects reported a local adverse event. The frequencies of systemic adverse events, overall, were similar during the three different observation periods.

Table 14. Study TC9704 Frequency of selected local and systemic adverse events that occurred during the first 72 hours following Td vaccination, by age group

Adverse Event	Age group[1]	Severity	n	%	95% CI
Redness	Adults	any	22	8.4	(5.3, 12.4)
		≥35 mm	4	1.5	(0.4, 3.8)
		≥50 mm	3	1.1	(0.2, 3.3)
		≥100 mm	1	0.4	(0.0, 2.1)
	Adolescents	any	2	5.4	(0.7, 18.2)
		≥35 mm	1	2.7	(0.1, 14.2)
		≥50 mm	1	2.7	(0.1, 14.2)
		≥100 mm	0	0.0	(0.0, 9.5)
Swelling[4]	Adults	any	35	13.3	(9.4, 18.0)
		≥35 mm	15	5.7	(3.2, 9.2)
		≥50 mm	10	3.8	(1.8, 6.9)
		≥100 mm	4	1.5	(0.4, 3.8)
	Adolescents	any	6	16.2	(6.2, 32.0)
		≥35 mm	5	13.5	(4.5, 28.8)
		≥50 mm	4	10.8	(3.0, 25.4)
		≥100 mm	1	2.7	(0.1, 14.2)
Pain	Adults	any	223	84.8	(79.9, 88.9)
		moderate[2] or worse	32	12.2	(8.5, 16.7)
		severe[3]	1	0.4	(0.0, 2.1)
	Adolescents	any	30	81.1	(64.8, 92.0)
		moderate[2] or worse	7	18.9	(8.0, 35.2)
		severe[3]	0	0.0	(0.0, 9.5)
Fever	Adults	>37.9°C	11	4.2	(2.1, 7.4)
		≥38.3°C	0	0.0	(0.0, 1.4)
		≥40.5°C	0	0.0	(0.0, 1.4)
	Adolescents	>37.9°C	1	2.7	(0.1, 14.2)
		≥38.3°C	0	0.0	(0.0, 9.5)
		≥40.5°C	0	0.0	(0.0, 9.5)
Chills	Adults	any	12	4.6	(2.4, 7.8)
		moderate[2] or worse	1	0.4	(0.0, 2.1)
		severe[3]	1	0.4	(0.0, 2.1)
	Adolescents	any	3	8.1	(1.7, 21.9)
		moderate[2] or worse	2	5.4	(0.7, 18.2)
		severe	0	0.0	(0.0, 9.5)

Sore/swollen joints	Adults	any	14	5.3	(2.9, 8.8)
		moderate[2] or worse	1	0.4	(0.0, 2.1)
		severe[3]	0	0.0	(0.0, 1.4)
	Adolescents	any	3	8.1	(1.7, 21.9)
		moderate[2] or worse	0	0.0	(0.0, 9.5)
		severe[3]	0	0.0	(0.0, 9.5)

[1] Adults ages 18-54 years, N=263; adolescents ages 12-17 years, N=37
[2] Moderate = interfered with activities, but did not require medical care or absenteeism
[3] Severe = incapacitating, unable to perform usual activities, required medical care or absenteeism
[4]Swelling was considered ≥100 mm in 2 subjects for whom size was not reported
Source: STN:103171/0.5005, Volume 1, pages 201-204 and page 234

Unsolicited adverse events Among the 300 subjects who received Td, unsolicited adverse events included swelling of the entire injected upper limb, reported in one subject (0.3%) and neck symptoms, reported in 11 (3.7%) subjects. Reported neck symptoms included soreness, stiffness, discomfort, and pain.

Withdrawals due to adverse events One subject who was assigned to receive Td followed by cP one month later, voluntarily withdrew from the study due to adverse events following vaccination with Td. At 24 hours post-vaccination, the subject reported redness and swelling of 25 mm and mild pain. At 72 hours, the redness and swelling had increased to 110 mm, and the subject reported moderate pain, diarrhea, severe chills, decreased energy, muscle pain (neck and "subaxillary"), and a bitter taste in the mouth. The muscle pain lasted 6 days and the bitter taste lasted one day. On follow-up at Day 10, the local redness and swelling were 90 mm and the systemic symptoms were improved. No further follow-up was recorded.

Serious adverse events *(all study groups).* There were three serious adverse events reported during the study. One subject who received Td, followed by cP one month later, had onset of abdominal pain 24 days following cP, and an appendectomy. One subject who received Td, followed by cP one month later, was hospitalized for abdominal pain and vomiting, of undetermined etiology, which had an onset 20 days after cP vaccination. One subject had onset of abdominal pain 35 days after TdcP, and underwent a cholecystectomy. No deaths were reported.

8.1.6 Reviewer's Comments and Conclusions on Study TC9704

1. In Study TC9704, there were no pre-specified criteria for demonstrating an adequate immune response to Td. Based on immunogenicity data from the historical study of Td in Canadian Armed Forces recruits ages 17-29 years (described subsequently in Section 9.5), the sponsor assumed that 95% of subjects would achieve a post-vaccination diphtheria antitoxin level ≥0.1 IU/ml and a post-vaccination tetanus antitoxin level ≥0.1 IU/ml. As discussed in comment #3 below, in Study TC9704, the expected seroprotection rate for diphtheria was not met in adults.

2. In assessing immunogenicity to tetanus toxoid in this study, it is important to note that approximately 94% of subjects, overall, who received Td had pre-immunization tetanus antitoxin levels equal to or greater than the protective level of 0.1 IU/ml. Thus, examining the proportion of subjects who achieved this level post-vaccination does not provide much information on the immunogenicity of the vaccine. More useful assessments of vaccine immunogenicity are to evaluate the proportion of subjects with tetanus antitoxin titers ≥1.0 IU/ml and the proportion of subjects who demonstrated a booster response. Approximately half of adults and approximately 10% of adolescents had a pre-vaccination tetanus antitoxin level ≥1.0 IU/ml; 98.9% of adults and all adolescents achieved this level post-vaccination. All

adolescents and approximately 80% of adults demonstrated a booster response for tetanus (≥4-fold increase in antibody level and a post-vaccination level ≥0.1 IU/ml). The lower booster response rate in adults relative to adolescents may reflect, in part, their higher pre-vaccination GMTs. However, further analyses to assess this possibility were not provided.

3. Approximately 38% of adults and 57% of adolescents had a pre-vaccination diphtheria antitoxin level ≥0.1 IU/ml. All adolescents and approximately 85% (lower bound of 95% CI = 80%) of adults achieved this level post-vaccination. Among 56 adults with a pre-vaccination diphtheria antitoxin level <0.01 IU/ml, the post-vaccination level was <0.1 IU/ml in 32 (57.1%), including three (5.4%) whose post-vaccination level remained <0.01 IU/ml. Similar findings were observed among 81 adults in the TdcP group who had a pre-vaccination diphtheria antitoxin level <0.01 IU/ml (data presented in a subsequent section of this review). Reasons for the lower than expected diphtheria seroprotection rate among adults are not clear. One potential explanation offered by the sponsor is the older age of the adults in Study TC9704 relative to subjects in the historical study among Canadian Armed Forces recruits, and the possibility that some adults in Study TC9704 had not been adequately primed. Alternatively, some adults who were adequately primed may have had a suboptimal response to booster vaccination. Data to reliably assess these possibilities are not available. The clinical relevance of the lower than expected diphtheria seroprotection rate among adults in Study TC9704 is unknown. In the absence of a control arm that received a U.S. licensed Td vaccine, this finding is difficult to interpret.

4. The apparently lower booster response rate for diphtheria in adults (78%) compared with adolescents (100%) may reflect inadequate priming in some adults, inadequate booster response in some adequately primed adults, and/or inability to achieve a four fold rise in antibody level in some subjects who had a high pre-vaccination level. The relative contribution of these and/or other factors, is not known. As with the lower than expected diphtheria seroprotection rate among adults, the clinical relevance of the observed booster response rate in adults is not known, and it is difficult to interpret this finding in the absence of a control group that received a U.S. licensed Td vaccine.

5. Local adverse events were reported frequently following Td vaccination. Most reports of pain were graded as mild or moderate in intensity and most occurrences of local swelling or redness were <50 mm. Approximately 4% of adults and approximately 11% of adolescents reported swelling ≥50 mm. There was a tendency towards a higher frequency of some local adverse events in females relative to males, although the study was not designed to assess gender differences.

6. Fever within 72 hours following Td vaccination was reported in approximately 6-8% of subjects. No subject who received Td reported fever ≥38.3°C. Approximately 5-8% of subjects reported chills or sore/swollen joints.

7. Although this study raised no particular safety concerns, interpretation of the safety data is limited by the absence of an appropriate control group.

8.2 TdcP-IPV Study TD9707 Safety and Immunogenicity of Td Combined with Three Lots of Component Pertussis Vaccine and Inactivated Poliomyelitis Vaccine Grown on Vero Cells (TdcP-IPV) in Adolescents and Adults Compared to one Lot of Td in Combination with Inactivated Poliomyelitis Vaccine Grown on MRC-5 Cells (Td-mIPV) Given Separately from One Lot of Component Pertussis (cP) Vaccine in Adolescents and One Lot of Td and One Lot of cP Vaccine Given Separately in Adults and One Lot of TdcP Vaccine Given Separately from Inactivated Poliomyelitis Vaccine Grown on Vero Cells (IPV) in Adults

8.2.1 Study Period February 1998 – July 1998

8.2.2 Objectives

Primary

- To compare the safety of TdcP-IPV in adolescents and adults with Td-mIPV and cP given separately one month apart in adolescents and compared to TdcP or Td given separately one month apart with IPV or cP in adults
- To compare the immunogenicity of TdcP-IPV in terms of seroprotection and seroconversion rates one month after a booster dose of TdcP with Td-mIPV and cP given separately one month apart in adolescents compared to TdcP or Td given separately one month apart with IPV or cP in adults

Secondary

- To test the consistency of 3 lots of TdcP-IPV in adolescents and adults in terms of safety and immunogenicity (seroprotection and seroconversion rates) one month after a booster dose.
- To assess and compare GMTs of each vaccine antigen given to the study groups
- To assess the safety and immunogenicity of two doses of cP given one month apart in adults

Observational

- To compare the safety and immunogenicity of TdcP with Td and cP given separately, with safety and immunogenicity of a similar lot of TdcP used in a previous trial, in order to bridge the data

8.2.3 Design: Phase II, randomized (by age cohort—adolescent and adult), single blinded (subjects blinded; study personnel not blinded), multi-center (six Canadian centers) controlled clinical trial involving six vaccines (Td-mIPV, Td, cP, IPV, TdcP, and TdcP-IPV) and 10 study groups. Three lots of TdcP-IPV and one lot of each of the other vaccines were used.

8.2.4 Protocol

Randomization Procedures: Computerized randomization employed a balanced block format stratified by age group, with equal probability into each of the four adolescent and six adult treatment groups. Separate randomizations were performed for each of the six sites. Four sites enrolled adolescents.

Table 15. Study TD9707 Study Groups

Group	Age Group	Vaccine(s)
1[1]	Adolescent[2]	TdmIPV → cP
2	Adolescent	TdcP1-IPV
3	Adolescent	TdcP2-IPV
4	Adolescent	TdcP3-IPV
5[1]	Adult[3]	Td → cP
6[1]	Adult	TdcP → IPV
7[1]	Adult	TdcP → cP
8	Adult	TdcP1-IPV
9	Adult	TdcP2-IPV
10	Adult	TdcP3-IPV

[1]Subjects in groups 1, 5, 6, and 7 received the study vaccines 28-35 days apart

[2] Adolescents ages 12-18 years

[3] The age range of enrolled adults, across all vaccine groups, was 19-65 years, although the protocol-defined upper age limit for inclusion in the study was 59 years. The age range of adults who received Td in Group 5 was 19-58 years.

Table 16. Study TD9707 Vaccines and lot numbers

Vaccine	Lot Number
Td	001-11
cP	1001-11
TdcP	21-11
TdcP1-IPV[1]	15001-11
TdcP2-IPV[1]	15002-11
TdcP3-IPV[1]	15003-11
IPV	M0534
Td-mIPV	34015-11

[1] Diphtheria Concentrate DCA-018 and Tetanus Concentrate TCA-012 were used to formulate all TdcP-IPV lots.
Source: STN:103171/0.5000, Volume 2, pages 37-38, and Volume 9, pages 124, 130, and 136

Table 17. Study TD9707 Vaccine contents per 0.5 ml dose

Components	Td	cP	IPV[1]	TdcP	TdcP-IPV[1]	Td-mIPV[2]
Tetanus toxoid	5 Lf			5 Lf	5 Lf	5 Lf
Diphtheria toxoid	2 Lf			2 Lf	2 Lf	2 Lf
Pertussis toxoid		2.5 µg		2.5 µg	2.5 µg	
Filamentous hemagglutinin (FHA)		5 µg		5 µg	5 µg	
Fimbriae 2+3		5 µg		5 µg	5 µg	
Pertactin		3 µg		3 µg	3 µg	
Aluminum phosphate	1.5 mg	1.5 mg		1.5 mg	1.5 mg	1.5 mg
2-phenoxyethanol	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%
Poliovirus type 1 (D Ag units)			40		40	40
Poliovirus type 2 (D Ag units)			8		8	8
Poliovirus type 3 (D Ag units)			32		32	32

Source: STN:103171/0.5000, Volume 2, pages 37-39
[1] Also contains tween 80, bovine serum albumin, trace formaldehyde, neomycin, streptomycin, and polymyxin B
[2] Also contains human albumin, tween 80, bovine serum, trace amounts of formaldehyde, neomycin, polymyxin B

Population: The study was conducted at four study centers in Canada.

Inclusion criteria

- age ≥12 years and <60 years
- informed consent obtained
- good health on basis of medical history
- able to cooperate with requirements of the study
- for females, use of an effective method of contraception during study and negative pregnancy test prior to vaccination OR post menopausal, OR only sexual partner sterilized (if male)

Exclusion criteria

- Pregnancy or planning a pregnancy during study period
- Known or suspected primary disease of the immune system
- Malignancy or receiving immunosuppressive therapy
- Receipt of any pertussis, polio, diphtheria, or tetanus containing vaccines within previous 5 years
- any significant underlying chronic disease
- known impairment of neurologic function or seizure disorder
- personal history of physician diagnosed or laboratory confirmed pertussis within the last 2 years
- receipt of blood products or immunoglobulin within the previous 3 months
- known or suspected allergy to any of the vaccines intended for use in the study or any vaccine

components including neomycin, streptomycin, and polymyxin B
- receipt of any vaccine within 2 weeks of receiving a study vaccine
- daily use of non-steroidal anti-inflammatory drugs

Reasons for deferring vaccination
- febrile illness within previous 72 hours; immunization deferred at least 48 hours.

Vaccination schedule: Subjects in groups 1, 5, 6, and 7 received the specified study vaccines 28-35 days apart. IPV was administered subcutaneously in the deltoid or triceps. All other study vaccines were injected intramuscularly, preferably into the deltoid.

Concomitant Vaccines: Neither specified or prohibited in the study protocol.

Endpoints relevant to the evaluation of Td:
- Proportion of subjects reporting specified local and general adverse events within 0-24 hours, 24-72 hours, and 72 hours to 14 days post-vaccination
- Proportion of subjects with post-immunization protective levels for tetanus antitoxin (≥0.1 IU/ml) and diphtheria antitoxin (≥0.1 IU/ml)
- Pre- and post-vaccination geometric mean antibody titers to tetanus and diphtheria toxins

Surveillance:

Safety: Safety monitoring was similar to the methods for Study TC9704, with the following exceptions: a) the total observation period for solicited adverse events was 14 days, except for fever which was monitored for the first 72 hours post-vaccination; and b) participant worksheets were provided to the sites to distribute to subjects for recording adverse events. Some sites used the provided template or a modified template for this purpose, and some sites used a modified template for their source documents.

Efficacy (Immunogenicity): A blood sample was obtained from each subject just prior to immunization and at 28-35 days following each immunization. Serum samples were tested for antibodies to tetanus toxin using an ELISA and for antibodies to diphtheria toxin using a ---------- assay (---------- method), as well as for antibodies to pertussis antigens and polioviruses (not relevant to this review). Assays were performed at Aventis Pasteur Limited.

Statistical plan: The statistical plan and sample size determinations were based on the objectives of comparing the safety and immunogenicity of TdcP-IPV relative to separate administration of antigens, and are of limited relevance to the evaluation of Td, which was used as a control vaccine in this study. It was assumed that at least 95% of subjects in the Td group would achieve a post-vaccination diphtheria antibody level ≥0.1 IU/ml and a post-vaccination tetanus antibody level ≥0.1 IU/ml, based on the historical study of Td conducted in Canadian Armed Forces recruits who ranged in age from 17-29 years. Using these cutoffs to define protective levels, for each antigen, a seroprotection rate ≥95% was considered clinically acceptable.

8.2.5 Results for Td vaccination for subjects in Study Group 5 (Td → cP)

8.2.5.1 Population: A total of 126 subjects (65.1% female) were enrolled in Study Group 5 and received Td vaccine. Their mean age was 37.9 years (range 19.4-58.5 years).

8.2.5.2 Immunogenicity*:* Results for study group 5 are presented in Tables 18-20.

Table 18. Study TD9707 Tetanus antitoxin responses, study group 5 (adults who received Td)[1]

GMT (IU/ml) (95% CI)		Booster response[2] rate, % (95% CI)	% with specified antibody concentration, IU/ml (95% CI)					
Pre	post			≥ 0.01		≥ 0.1		≥ 1.0	
				%	(95% CI)	%	(95% CI)	%	(95% CI)
0.95	12.65	81.15	Pre	99.2	(95.5, 100.0)	92.6	(86.5, 96.6)	59.0	(49.7, 67.8)
(0.75, 1.18)	(10.59, 5.11)	(73.1, 87.7)	Post	100.0	(97.0, 100.0)	100.0	(97.0, 100.0)	96.7	(91.8, 99.1)

[1] Analysis based on 122 subjects

[2] Booster response is defined as a ≥ 4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 IU/ml must also have a post-vaccination level ≥ 0.1 IU/ml to be considered a responder.

Source: STN:103171/0.5020, page 3

The tetanus booster response rate following Td tended to be higher in females (86.1%) compared with males (72.1%). However, the proportion of subjects with tetanus antitoxin levels ≥ 0.1 IU/ml and ≥ 1.0 IU/ml post-vaccination were similar in females and males.

Table 19. Study TD9707 Diphtheria antitoxin responses, study group 5 (adults who received Td)[1]

GMT (95% CI)		Booster response[2] rate, % (95% CI)	% with specified antibody concentration, IU/ml (95% CI)		
pre	post		≥ 0.01	≥ 0.1	≥ 1.0
0.05 (0.03, 0.07)	0.94 (0.7, 1.3)	83.6 (75.8, 89.7)	pre 82.8 (74.9, 89.0) post 98.4 (94.2, 99.8)	pre 35.2 (26.8, 44.4) post 89.3 (82.5, 94.2)	pre 6.6 (2.9, 12.5) post 59.0 (49.7, 67.8)

[1] Analysis based on 122 subjects

[2] Booster response is defined as a ≥ 4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 IU/ml must also have a post-vaccination level ≥ 0.1 IU/ml to be considered a responder.

Source: STN:103171/0.5000, Volume 1, page 43 and Volume 2, pages 253-254 and page 271; STN:103171/0.5005, Volume 1, pages 241, 246

The diphtheria antitoxin responses appeared to be similar in males and females who received Td.

Table 20. Study TD9707 Proportion of subjects with specified levels of diphtheria antitoxin post-vaccination, stratified by pre-vaccination diphtheria antitoxin level, study group 5 (adults who received Td)

		Post-vaccination diphtheria antitoxin level (IU/ml)					
		≥ 0.01			≥ 0.1		
Pre-vaccination level (IU/ml)	N	n	%	(95 % CI)	n	%	(95 % CI)
<0.01	21	19	90.5	(69.6, 98.8)	11	52.4	(29.8, 74.3)
0.01-<0.1	58	58	100.0	(93.8, 100.0)	55	94.8	(85.6, 98.9)

Source: STN:103171/0.5005, Volume 1, page 243

8.2.5.3 Safety: The frequencies of local and systemic adverse events reported during the first 72 hours following vaccination with Td are presented in Table 21. Data were also provided on adverse events that occurred during the three specified observation periods post-vaccination (0-24 hours, 24-72 hours, and 72 hours-14 days). Overall, the frequency of any local adverse event was greatest during the 0-24 hour post-vaccination period, and declined during the two subsequent periods. For example, for the three observation periods, the frequencies of any local adverse event were 87%, 46%, and 7%, respectively. This temporal trend was observed for redness and pain. However, the frequency of swelling did not decline until the third observation period. For systemic adverse events, overall reported frequencies were similar at the 0-24 hour and 72 hour-14 day observation points, and slightly lower at the 24-72 hour point. The frequency of any pain and moderate or severe pain tended to be higher in females than males (89.0% vs. 77.3% for any pain; 18.3% vs. 9.1% for moderate or severe pain). The frequencies of other adverse events were generally similar in females and males who received Td.

Table 21. Study TD9707 Frequency of selected local and systemic adverse events that occurred during the first 72 hours following Td vaccination among adults in study group 5[1] (N=126)

Adverse event	Severity[2]	n	(%)	[95% CI]
Redness	Any	27	(21.4)	[14.6, 29.6]
	≥35 mm	4	(3.2)	[0.9, 7.9]
	≥50 mm	0	(0.0)	[0.0, 2.9]
	≥100 mm	0	(0.0)	[0.0, 2.9]
Swelling	Any	13	(10.3)	[5.6, 17.0]
	≥35 mm	9	(7.1)	[3.3, 13.1]
	≥50 mm	5	(4.0)	[1.3, 9.0]
	≥100 mm	1	(0.8)	[0.0, 4.3]
Pain	Any	107	(84.9)	[77.5, 90.7]
	moderate[2] or worse	19	(15.1)	[9.3, 22.5]
	severe[3]	1	(0.8)	[0.0, 4.3]
Fever[4]	Any	1	(0.8)	[0.0, 4.3]
	moderate or worse	0	(0.0)	[0.0, 2.9]
	severe	0	(0.0)	[0.0, 2.9]
Chills	Any	7	(5.6)	[2.3, 11.1]
	moderate[2] or worse	0	(0.0)	[0.0, 2.9]
	severe[3]	0	(0.0)	[0.0, 2.9]
Sore/Swollen Joints	Any	7	(5.6)	[2.3, 11.1]
	moderate[2] or worse	4	(3.2)	[0.9, 7.9]
	severe[3]	0	(0.0)	[0.0, 2.9]

Source: STN:103171/0.5005, Volume 1, pages 259-262

[1] There were 126 subjects in study group 5; denominators may vary slightly due to missing data

[2] Moderate = interfered with activities, but did not require medical care or absenteeism

[3] Severe = incapacitating, unable to perform usual activities, required medical care or absenteeism

[4] Severe fever = oral temperature ≥40.5° C; moderate fever = oral temperature ≥38.9° C

Among subjects in all vaccine groups, three serious adverse events, including one death, were reported during the study.

- A 12 year old male, who received Td-mIPV followed by cP one month later, experienced a tonic-clonic seizure. The subject had no previous history of seizures. During the first 24 hours following Td-mIPV, the subject reported mild pain at the injection site. Following cP vaccination, the only solicited adverse event reported was mild tiredness/decreased energy level within 72 hours post-vaccination. Thirty days following cP, the subject experienced a tonic-clonic seizure that lasted 1-2 minutes, with a 45-minute post-ictal period (unresponsive for 30 minutes). A physical examination

was normal. An electroencephalogram demonstrated generalized spikes with an abnormal background, consistent with idiopathic generalized seizure. A CT scan of the head was normal. No anticonvulsants were prescribed as per the family's decision after consultation with a neurologist. No follow-up information was provided. The subject's case report form also indicates a fracture of the left radius ">14 days" following cP.

- One subject with a history of depression was hospitalized for suicidal ideation 17 days post-vaccination with TdcP-IPV.
- One subject died of metastatic breast cancer 9 months after immunization with TdcP-IPV.

8.2.6 Reviewer's Comments and Conclusions on Study TD9707

1. In the study protocol, seroprotection rates of 95% for tetanus and diphtheria were considered clinically acceptable. However, these seroprotection rates were not stated as formal endpoints for the evaluation of Td, and there were no pre-specified criteria for demonstrating an adequate immune response to Td.

2. The immunogenicity results for tetanus and diphtheria among adults who received Td in this study are similar to those observed in Study TC9704. Thus, conclusions on immunogenicity data from adults in Study TC9704 also apply to this study.

3. Although no adolescents in this study received Td, of note is that there were 17 adolescents in the TdcP-IPV group who had a pre-vaccination diphtheria antitoxin level <0.01 IU/ml. Of these adolescents, 9 (52.9%) had a post-vaccination level <0.1 IU/ml, including one whose level remained <0.01 IU/ml (data on TdcP-IPV recipients presented in a subsequent section of this review). Assuming that adolescents had been adequately primed for tetanus and diphtheria, these data raise the concern of inadequate booster responses to tetanus and diphtheria toxoids in some adolescents who received TdcP-IPV. However, the relevance of this finding to Td booster vaccination is not known.

4. Local adverse events were reported frequently following Td vaccination. Most reports of pain were graded as mild or moderate in intensity and most occurrences of local swelling or redness were <50 mm. Approximately 5% of subjects reported swelling ≥50 mm. The frequency of local adverse events was highest during the first 24 hours post-vaccination, with evidence for resolution of most events by 14 days post-vaccination.

6. Most systemic adverse events were mild in intensity. The similar frequency of some systemic adverse events within 24 hours post-vaccination, and during the 72 hour-14 day period post-vaccination may reflect the non-specific nature of some events as well as the longer duration of the latter observation period. Fever was reported infrequently.

7. The nature and timing of the serious adverse events reported during the course of the study suggest that they were unlikely attributable to vaccination with a Td-containing vaccine.

8. Although this study raised no particular safety concerns, interpretation of the safety data are hindered by the absence of an appropriate control group.

9. SUPPLEMENTAL CLINICAL DATA ON BOOSTER IMMUNIZATION

9.1 TdcP Study TC9704

9.1.1 Supplemental immunogenicity data from TdcP groups

Table 22. Study TC9704 Tetanus GMTs (IU/ml) pre- and one month post-immunization, by age group, subjects who received TdcP[1]

	Pre			Post		
Group	N	GMT	(95% CI)	N	GMT	(95% CI)
Adults[2]	393	1.01	(0.89, 1.14)	391	12.52	(11.56, 13.55)
Adolescents[3]	55	0.42	(0.32, 0.55)	55	20.93	(16.09, 27.22)

[1]Includes all three TdcP lots
[2] ages 18-54 years
[3]ages 12-17 years
Source: STN:103171/0.5020, page 4

Table 23. Study TC9704 Proportion of subjects with specified levels of tetanus antibody, pre- and 1-month post-immunization, adolescents and adults who received TdcP[1]

			≥ 0.01 IU/ml		≥ 0.1 IU/ml		≥ 1.0 IU/ml	
Group		N	%	(95% CI)	%	(95% CI)	%	(95% CI)
Adults[2]	pre	393	98.2	(96.4, 99.3)	96.2	(93.8, 97.8)	57.0	(51.9, 62.0)
	post	391	100.0	(99.1, 100.0)	99.7	(98.6, 100.0)	99.2	(97.8, 99.8)
Adolescents[3]	pre	55	100.0	(93.5, 100.0)	90.9	(80.0, 97.0)	14.5	(6.5, 26.7)
	post	55	100.0	(93.5, 100.0)	100.0	(93.5, 100.0)	100.0	(93.5, 100.0)

[1]Includes all three TdcP lots
[2] ages 18-54 years
[3]ages 12-17 years
Source: STN:103171/0.5020, page 5

Table 24. Study TC9704 Percent of subjects with a booster resonse[1] to tetanus toxoid following vaccination with TdcP[2]

Group	N	%	(95 % CI)
Adults[3]	391	79.80	(75.5, 83.7)
Adolescents[4]	55	96.36	(87.5, 99.6)

[1] Booster response is defined as a ≥ 4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 IU/ml must also have a post-vaccination level ≥ 0.1 IU/ml to be considered a responder.
[2]Includes all three TdcP lots
[3] ages 18-54 years
[4]ages 12-17 years
Source: STN:103171/0.5020, page 5

Table 25. Study TC9704 Diphtheria GMTs (IU/ml) pre- and one month post-immunization, by age group, subjects who received TdcP[1]

	Pre		Post	
Group	N	GMT (95% CI)	N	GMT (95% CI)
Adults[2]	394	0.03 (0.03, 0.04)	391	0.60 (0.49, 0.72)
Adolescents[3]	55	0.10 (0.06, 0.16)	55	11.8 (7.31, 19.1)

[1]Includes all three TdcP lots
[2]ages 18-54 years
[3]ages 12-17 years
Source: STN:103171/0.5000, Volume 1, page 133-134

Table 26. Study TC9704 Proportion of subjects with specified levels of diphtheria antibody, pre- and 1-month post-immunization, adolescents and adults who received TdcP[1]

Group	Timing	N	≥ 0.01 IU/ml % (95 % CI)	≥ 0.1 IU/ml % (95 % CI)	≥ 1.0 IU/ml % (95 % CI)
Adults[2]	pre	394	79.4 (75.1, 83.3)	26.4 (22.1, 31.0)	2.3 (1.0, 4.3)
	post	391	97.7 (95.7, 98.9)	83.1 (79.0, 86.7)	43.5 (38.5, 48.6)
Adolescents[3]	pre	55	92.7 (82.4, 98.0)	41.8 (28.7, 55.9)	9.1 (3.0, 20.0)
	post	55	100 (93.5, 100.0)	98.2 (90.3, 100.0)	89.1 (77.8, 95.9)

[1]Includes all three TdcP lots
[2]ages 18-54 years
[3]ages 12-17 years
Source: STN:103171/0.5005, Volume 1, page 187

Table 27. Study TC9704 Proportion of subjects with specified levels of diphtheria antitoxin following vaccination with TdcP[1], by pre-vaccination diphtheria antitoxin level and age group.

			Post-vaccination diphtheria antitoxin level (IU/ml)	
			≥ 0.01	≥ 0.1
Group	pre-vaccination level (IU/ml)	N	n % (95 % CI)	n % (95 % CI)
Adults[2]	<0.01	81	72 88.9 (80.0, 94.8)	29 35.8 (25.4, 47.2)
	0.01-<0.1	207	207 100 (98.2, 100)	98 93.2 (88.9, 96.3)
Adolescents[3]	<0.01	4	4 100 (39.8, 100)	3 75.0 (19.4, 99.4)
	0.01-<0.1	28	28 100 (87.7, 100)	28 100 (87.7, 100)

[1]Includes all 3 lots of TdcP
[2]ages 18-54 years
[3]ages 12-17 years
Source: STN:103171/0.5005, Volume 1, page 189

Table 28. Study TC9704 Proportion of subjects with a booster response[1] to diphtheria toxoid following vaccination with TdcP[2]

Group	N	n % (95 % CI)
Adults[3]	391	301 77.0 (72.5, 81.1)
Adolescents[4]	55	53 96.4 (87.5, 99.6)

[1] Booster response is defined as a ≥ 4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 IU/ml must also have a post-vaccination level ≥ 0.1 IU/ml to be considered a responder.
[2]Includes all three TdcP lots
[3] ages 18-54 years
[4]ages 12-17 years
Source: STN:103171/0.5005, Volume 1, page 191

9.1.2 Supplemental safety data from TdcP groups

Table 29. Study TC9704 Frequency of selected local and systemic adverse events that occurred during the first 72 hours following TdcP vaccination, by age group

Adverse Event	Age group[1]	Severity	n	%	95% CI
Redness	Adults	any	40	10.2	(7.4, 13.6)
		≥35 mm	7	1.8	(0.7, 3.6)
		≥50 mm	4	1.0	(0.3, 2.6)
		≥100 mm	0	0.0	(0.0, 0.9)
	Adolescents	any	9	16.4	(7.8, 28.8)
		≥35 mm	7	12.7	(5.3, 24.5)
		≥50 mm	4	7.3	(2.0, 17.6)
		≥100 mm	2	3.6	(0.4, 12.5)
Swelling[4]	Adults	any	57	14.5	(11.2. 18.4)
		≥35 mm	32	8.1	(5.6, 11.3)
		≥50 mm	18	4.6	(2.7, 7.1)
		≥100 mm	3	0.8	(0.2, 2.2)
	Adolescents	any	14	25.5	(14.7, 39.0)
		≥35 mm	11	20.0	(10.4, 33.0)
		≥50 mm	9	16.4	(7.8, 28.8)
		≥100 mm	2	3.6	(0.4, 12.5)
Pain	Adults	any	341	86.8	(83.0, 90.0)
		moderate[2] or worse	65	16.5	(13.0. 20.6)
		severe[3]	2	0.5	(0.1, 1.8)
	Adolescents	any	53	96.4	(87.5, 99.6)
		moderate[2] or worse	18	32.7	(20.7, 46.7)
		severe[3]	0	0.0	(0.0, 6.5)
Fever	Adults	>37.9°C	26	6.6	(4.4, 9.6)
		≥38.3°C	5	1.3	(0.4, 3.0)
		≥40.5°C	0	0.0	(0.0, 0.9)
	Adolescents	>37.9°C	6	10.9	(4.1, 22.2)
		≥38.3°C	2	3.6	(0.4, 12.5)
		≥40.5°C	0	0.0	(0.0, 6.5)
Chills	Adults	any	30	7.6	(5.2, 10.7)
		moderate[2] or worse	5	1.3	(0.4, 2.9)
		severe[3]	1	0.3	(0.0, 1.4)
	Adolescents	any	12	21.8	(11.8, 35.0)
		moderate[2] or worse	3	5.5	(1.1, 15.1)
		severe	1	1.8	(0.0, 9.7)

Sore/swollen joints	Adults	any	31	7.9	(5.4, 11.0)
		moderate[2] or worse	6	1.5	(0.6, 3.3)
		severe[3]	2	0.5	(0.1, 1.8)
	Adolescents	any	2	3.6	(0.4, 12.5)
		moderate[2] or worse	1	1.8	(0.0, 9.7)
		severe[3]	0	0.0	(0.0, 6.5)

[1] Adults ages 18-54 years, N=393; adolescents ages 12-17 years, N=55
[2] Moderate = interfered with activities, but did not require medical care or absenteeism
[3] Severe = incapacitating, unable to perform usual activities, required medical care or absenteeism
[4]Swelling was set as ≥100 mm in 2 subjects for whom size was not reported
Source: STN:103171/0.5005, Volume 1, pages 205-208

9.1.3 Reviewer's Comments and Conclusions on Supplemental Data from Study TC9704

- Among adolescents enrolled in Study TC9704, the frequency of fever and local adverse events tended to be higher in those who received TdcP relative to those who received Td. Among adults, the safety data for subjects in the TdcP vaccine groups were similar to those for subjects who received Td.

- The proportion of adults in the TdcP groups who achieved a post-vaccination diphtheria antitoxin level ≥1.0 IU/ml was somewhat lower than that observed among adults in the Td groups. In all other immunogenicity analyses, the results were similar for subjects who received Td or TdcP.

9.2 TdcP-IPV Study TD9707

9.2.1 Study population (groups that received vaccines other than Td)

Table 30. TD9707 Study population-- subjects in Td-mIPV, TdcP, and TdcP-IPV study groups

	Adolescents		Adults	
	Td-mIPV	TdcP-IPV[1]	TdcP[2]	TdcP-IPV[3]
N	116	350	244	366
Mean age (years)[4]	13.9	~14	~38	~38
Age range (years)	12-16	12-18	18-60	19-65
% male	53	51	31	30

[1] Includes subjects who received three different lots of TdcP-IPV (Groups 2, 3, and 4)
[2] Includes subjects who received either IPV or cP one month later (Groups 6 and 7)
[3] Includes subjects who received three different lots of TdcP-IPV (Groups 8, 9, and 10)
[4] For vaccines for which there was more than one study group, approximate mean ages are given because combined data were not available.
Source: STN:103171/0.5000, Volume 2, page 58

9.2.2 Supplemental immunogenicity data from Td-mIPV, TdcP, and TdcP-IPV study groups

Table 31. Study TD9707 Tetanus GMTs (IU/ml) pre- and one month post-immunization, by age group, subjects who received Td-mIPV, TdcP, or TdcP-IPV

	Pre			Post		
	N	GMT	(95% CI)	N	GMT	(95% CI)
Adults TdcP[1]	240	0.91	(0.78, 1.07)	240	13.77	(12.35, 15.35)
TdcP-IPV[2]	364	0.90	(0.79, 1.02)	364	9.96	(9.15, 10.84)
Adolescents Td-mIPV	116	0.53	(0.44, 0.65)	116	15.67	(13.39, 18.34)
TdcP-IPV[2]	348	0.52	(0.46, 0.59)	348	14.88	(13.50, 16.40)

[1] Groups 6 and 7 combined
[2]Includes all three TdcP-IPV lots
Source: STN:103171/0.5020, page 5

Table 32. Study TD9707 Proportion of subjects with specified levels of tetanus antibody, pre- and 1-month post-immunization, subjects who received Td-mIPV, TdcP, or TdcP-IPV

Study Group		N	≥ 0.01 IU/ml			≥ 0.1 IU/ml			≥ 1.0 IU/ml		
			n	%	(95 % CI)	n	%	(95 % CI)	n	%	(95 % CI)
Adults											
TdcP[1]	Pre	240	238	99.2	(97.0, 99.9)	224	93.3	(89.4, 96.1)	129	53.8	(47.2, 60.2)
	Post	240	240	100.0	(98.5, 100.0)	240	100.0	(98.5, 100.0)	239	99.6	(97.7, 100.0)
TdcP-IPV[2]	Pre	364	361	99.2	(97.6, 99.8)	339	93.1	(90.0, 95.5)	193	53.0	(47.8, 58.2)
	Post	364	364	100.0	(99.0, 100.0)	364	100.0	(99.0, 100.0)	360	98.9	(97.2, 99.7)
Adolescents											
Td-mIPV	Pre	116	116	100.0	(96.9, 100.0)	109	94.0	(88.0, 97.5)	32	27.6	(19.7, 36.7)
	Post	116	116	100.0	(96.9, 100.0)	116	100.0	(96.9, 100.0)	116	100.0	(96.9, 100.0)
TdcP-IPV[2]	Pre	348	348	100.0	(98.9, 100.0)	326	93.7	(90.6, 96.0)	86	24.7	(20.3, 29.6)
	Post	348	348	100.0	(98.9, 100.0)	348	100.0	(98.9, 100.0)	346	99.4	(97.9, 99.9)

[1] Groups 6 and 7 combined
[2]Includes all three TdcP-IPV lots
Source: STN:103171/0.5020, page 6

Table 33. Study TD9707 Proportion of subjects with a booster response[1] to tetanus toxoid, by study group, subjects who received Td-mIPV, TdcP, or TdcP-IPV

Study Group	N	n	%	(95 % CI)
Adults				
TdcP[2]	240	200	83.3	(78.0, 87.8)
TdcP-IPV[3]	364	281	77.2	(72.5, 81.4)
Adolescents				
TdmIPV	116	109	94.0	(88.0, 97.5)
TdcP-IPV[3]	348	316	90.8	(87.3, 93.6)

[1] Booster response is defined as a ≥ 4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 IU/ml must also have a post-vaccination level ≥ 0.1 IU/ml to be considered a responder.
[2] Groups 6 and 7 combined
[3]Includes all three TdcP-IPV lots
Source: STN:103171/0.5020, page 6

Table 34. Study TD9707 Diphtheria GMTs (IU/ml) pre- and one month post-immunization, by age group, subjects who received Td-mIPV, TdcP, or TdcP-IPV

	Pre		Post	
	N	GMT (95% CI)	N	GMT (95% CI)
Adults				
TdcP[1]	120	0.04 (0.03, 0.06)	120	0.92 (0.67, 1.27)
TdcP[2]	118	0.04 n/a	119	0.63 n/a
TdcP-IPV[3]	364	0.04 (0.03, 0.05)	364	0.49 (0.40, 0.59)
Adolescents				
Td-mIPV	116	0.15 (0.11, 0.20)	116	3.4 (2.6, 4.3)
TdcP-IPV[3]	348	0.09 (0.08, 0.11)	348	1.8 (1.6, 2.1)

[1] Group 6 (TdcP→IPV)
[2]Group 7 (TdcP→cP); confidence intervals not provided for this group
[3]Includes all three TdcP-IPV lots
n/a indicates not available
Source: STN:103171/0.5000, Volume 2, pages 98 and 271-272

Table 35. Study TD9707 Proportion of subjects with specified levels of diphtheria antibody, pre- and 1-month post-immunization, subjects who received Td-mIPV, TdcP, or TdcP-IPV

Study Group		N	≥ 0.01 IU/ml			≥ 0.1 IU/ml			≥ 1.0 IU/ml		
			n	%	(95 % CI)	n	%	(95 % CI)	n	%	(95 % CI)
Adults											
TdcP	Pre	238	184	77.3	(71.5, 82.5)	73	30.7	(24.9, 37.0)	11	4.6	(2.3, 8.1)
	Post	238	233	97.9	(95.2, 99.3)	203	85.3	(80.1, 89.5)	129	54.2	(47.6, 60.7)
TdcP-IPV	Pre	364	281	77.2	(72.5, 81.4)	115	31.6	(26.8, 36.6)	17	4.7	(2.7, 7.4)
	Post	364	350	96.2	(93.6, 97.9)	305	83.8	(79.6, 87.4)	128	35.2	(30.3, 40.3)
Adolescents											
TdmIPV	Pre	116	108	93.1	(86.9, 97.0)	78	67.2	(57.9, 75.7)	19	16.4	(10.2, 24.4)
	Post	116	115	99.1	(95.3, 100.0)	115	99.1	(95.3, 100.0)	102	87.9	(80.6, 93.2)
TdcP-IPV	Pre	348	331	95.1	(92.3, 97.1)	179	51.4	(46.0, 56.8)	23	6.6	(4.2, 9.8)
	Post	348	347	99.7	(98.4, 100.0)	338	97.1	(94.8, 98.6)	256	73.6	(68.6, 78.1)

Source: STN:103171/0.5005, Volume 1, page 241

Table 36. Study TD9707 Proportion of subjects with specified levels of diphtheria antitoxin post-vaccination, stratified by pre-vaccination diphtheria antitoxin level and study group, subjects who received Td-mIPV, TdcP, or TdcP-IPV

			Post-vaccination diphtheria antitoxin level (IU/ml)					
			≥ 0.01			≥ 0.1		
Study Group	Pre-vaccination level (IU/ml)	N	n	%	(95 % CI)	n	%	(95 % CI)
Adults								
TdcP	<0.01	54	49	90.7	(79.7, 96.9)	22	40.7	(27.6, 55.0)
	0.01-<0.1	111	111	100.0	(96.7, 100.0)	108	97.3	(92.3, 99.4)
TdcP-IPV	<0.01	83	69	83.1	(73.3, 90.5)	33	39.8	(29.2, 51.1)
	0.01-<0.1	166	166	100.0	(97.8, 100.0)	157	94.6	(90.0, 97.5)
Adolescents								
TdmIPV	<0.01	8	7	87.5	(47.3, 99.7)	7	87.5	(47.3, 99.7)
	0.01-<0.1	30	30	100.0	(88.4, 100.0)	30	100.0	(88.4, 100.0)
TdcP-IPV	<0.01	17	16	94.1	(71.3, 99.9)	8	47.1	(23.0, 72.2)
	0.01-<0.1	152	152	100.0	(97.6, 100.0)	151	99.3	(96.4, 100.0)

Source: STN:103171/0.5005, Volume 1, page 243

Table 37. Study TD9707 Proportion of subjects with a booster response[1] to diphtheria toxoid, by study group, subjects who received Td-mIPV, TdcP, or TdcP-IPV

Study Group	N	n	%	(95 % CI)
Adults				
TdcP	238	189	79.4	(73.7, 84.4)
TdcP-IPV	364	262	72.0	(67.1, 76.5)
Adolescents				
TdmIPV	116	112	96.6	(91.4, 99.1)
TdcP-IPV	348	315	90.5	(86.9, 93.4)

[1] Booster response is defined as a ≥ 4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 IU/ml must also have a post-vaccination level ≥0.1 IU/ml to be considered a responder.
Source: STN:103171/0.5005, Volume 1, page 246

9.2.3 Supplemental safety data from Td-mIPV, TdcP, and TdcP-IPV groups

Table 38. Study TD9707 Frequency of selected local and systemic adverse events during the first 72 hours following vaccination, subjects who received TdcP, TdcP-IPV, or TdmIPV

		TdcP (adults) N[1] = 244	TdcP-IPV (adults) N[1] = 366	TdcP-IPV (adolescents) N[1] = 349	TdmIPV (adolescents) N[1] = 116
Adverse event	Severity[4]	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Redness	any	23.4 (18.2, 29.2)	22.7 (18.5, 27.3)	16.9 (13.1, 21.3)	17.2 (10.9, 25.4)
	≥35 mm	5.3 (2.9, 8.9)	3.6 (1.9, 6.0)	2.6 (1.2, 4.8)	2.6 (0.6, 7.4)
	≥50 mm	3.3 (1.4, 6.4)	1.4 (0.4, 3.2)	1.4 (0.5, 3.3)	2.6 (0.6, 7.4)
	≥100 mm	0.8 (0.1 2.9)	0.3 (0.0, 1.5)	0.0 (0.0, 1.1)	0.9 (0.0, 4.7)
Swelling	any	15.2 (10.9, 20.3)	16.4 (12.7, 20.6)	21.8 (17.6, 26.5)	22.4 (15.2, 31.1)
	≥35 mm	7.0 (4.1, 10.9)	7.9 (5.4, 11.2)	11.7 (8.6, 15.6)	8.6 (4.2, 15.3)
	≥50 mm	4.1 (2.0, 7.4)	5.7 (3.6, 8.6)	6.6 (4.2, 9.7)	6.0 (2.5, 12.0)
	≥100 mm	1.2 (0.3, 3.6)	0.8 (0.2, 2.4)	1.7 (0.6, 3.7)	0.9 (0.0, 4.7)
Pain	any	84.8 (79.7, 89.1)	86.3 (82.4, 89.7)	88.3 (84.4, 91.4)	93.1 (86.9, 97.0)
	moderate or worse	17.6 (13.1, 23.0)	17.5 (13.7, 21.8)	33.0 (28.0, 38.2)	21.6 (14.5, 30.1)
	severe	1.2 (0.3, 3.6)	0.5 (0.1, 2.0)	1.7 (0.6, 3.7)	0.9 (0.0, 4.7)
Fever	any	4.9 (2.6, 8.4)	2.7 (1.3, 5.0)	14.2 (10.7, 18.3)	4.3 (1.4, 9.8)
	≥38.9°C	0.8 (0.1, 2.9)	0.8 (0.2, 2.4)	5.2 (3.1, 8.1)	2.6 (0.5, 7.4)
	≥40.5°C	0.0 (0.0, 1.5)	0.0 (0.0, 1.0)	0.3 (0.0, 1.6)	0.0 (0.0, 3.1)
Chills	any	7.4 (4.4, 11.4)	6.0 (3.8, 9.0)	16.3 (12.6, 20.6)	14.7 (8.8, 22.4)
	moderate or worse	2.0 (0.7, 4.7)	1.4 (0.4, 3.2)	3.4 (1.8, 5.9)	6.9 (3.0, 13.1)
	severe	0.4 (0.0, 2.3)	0.3 (0.0, 1.5)	0.6 (0.1, 2.1)	0.0 (0.0, 3.1)

Sore/Swollen joints	any	8.6 (5.4, 12.9)	6.6 (4.2, 9.6)	9.7 (6.8, 13.3)	11.2 (6.1, 18.4)
	moderate or worse	2.0 (0.7, 4.7)	1.6 (0.6, 3.5)	2.9 (1.4, 5.2)	0.9 (0.0, 4.7)
	severe	0.0 (0.0, 1.5)	0.0 (0.0, 1.0)	0.0 (0.0, 1.1)	0.0 (0.0, 3.1)

Source: STN:103171/0.5005, Volume 1, pages 259-265
[1] denominators may vary slightly due to missing data.
[2] moderate = interfered with activities, but did not require medical care or absenteeism; severe = incapacitating, unable to perform usual activities, required medical care or absenteeism

9.2.4 Reviewer's Comments and Conclusions on Supplemental Data from Study TD9707

- The booster response rate to diphtheria toxoid among adults who received TdcP-IPV was somewhat lower than in adults who received Td. Otherwise, the immunogenicity data from adults in the TdcP group were similar to data from adults who received Td in this study.
- There was a tendency towards a higher frequency of local swelling and fever in adults who received TdcP or TdcP-IPV compared with adults who received Td.

9.3 Study TD9805 Safety and Immunogenicity of TdcP Vaccine Compared to TdcP Vaccine and Hepatitis B Vaccine Given Concurrently in Adolescents 11-14 Years of Age

9.3.1 Study Period September 1998-August 1999

9.3.2 Objectives

Primary: Determine the safety and immunogenicity of TdcP vaccine compared to TdcP and hepatitis B vaccine administered concurrently in adolescents 11-14 years of age
Secondary: Determine whether concurrent administration of TdcP and hepatitis B vaccines at 11-14 years of age results in detectable immunologic interactions between components of the two vaccines.

9.3.3 Design: Phase II, open label, two groups, randomized, controlled clinical trial.

Study Groups: Subjects in Group 1 received TdcP and the first dose of hepatitis B vaccine separately, one month apart. Subjects in Group 2 received TdcP and the first dose of hepatitis B vaccine concurrently at separate administration sites.

Vaccines: The TdcP formulation was the same as that used in Study TC9704. Hepatitis B Vaccine (Recombivax HB®), manufactured by Merck, contains 5 μg of HBsAg per 0.5 ml dose, thimerosal (1:20,000) as a preservative, and aluminum hydroxide as an adjuvant.

9.3.4 Protocol

Population: The study was conducted at one study center in Surrey, British Columbia
Inclusion criteria

- age ≥11 years and <14 years
- informed consent obtained
- good health on basis of medical history
- plan to remain in study area for duration of the study
- all minors had a parent or legal guardian who could read, write, and understand English or French

Exclusion criteria

- Pregnancy. A pregnancy test was performed on all females at the time of enrollment.
- Known or suspected primary disease of the immune system
- Malignancy or receiving immunosuppressive therapy
- Receipt of any pertussis, diphtheria, or tetanus containing vaccines within previous 5 years

- any significant underlying chronic disease
- known impairment of neurologic function or seizure disorder
- personal history of physician diagnosed or laboratory confirmed pertussis within the last 2 years
- receipt of blood products or immunoglobulin within the previous 3 months
- known or suspected allergy to any of the vaccines intended for use in the study
- receipt of any vaccine within 2 weeks of receiving a study vaccine
- daily use of non-steroidal anti-inflammatory drugs

Reasons for deferring vaccination

- febrile illness within previous 72 hours; immunization deferred at least 48 hours.

Contraindications for second immunization

- anaphylactic reaction within 48 hours following immunization

Vaccination schedule: Group 1 was immunized at visit 1 with TdcP only, followed by hepatitis B immunization one month later. Group 2 was immunized at their first study visit (referred to as visit 2) with TdcP and hepatitis B given concurrently. For both groups, the second and third dose of hepatitis B vaccine were given 1 month and 6 months, respectively, after the initial hepatitis B vaccination. Vaccines were injected intramuscularly into the deltoid.

Endpoints/statistical considerations

- The sample size was based on an evaluation of immune response to the pertussis antigens.
- The primary safety evaluation involved an observational comparison of solicited local and systemic adverse events between recipients of TdcP and recipients of TdcP + hepatitis B vaccine given concurrently. For each adverse event, the difference between groups and two-sided 90% confidence interval on the difference was calculated.
- The primary immunogenicity evaluation included a comparison of the proportion of subjects in each vaccine group with one month post-immunization levels of tetanus and diphtheria antitoxin $\geq$0.01 IU/ml, $\geq$0.1 IU/ml, and $\geq$1.0 IU/ml. For tetanus and diphtheria, seroprotection was defined as an antibody level $\geq$0.1 IU/ml. Differences in seroprotection rates and two-sided 90% confidence intervals on the differences were calculated. For each antigen, a seroprotection rate of $\geq$95% was considered clinically acceptable. Pertussis antibody responses were also analyzed.
- The evaluation of the immune response to hepatitis B vaccine was considered a secondary analysis. A hepatitis B surface antigen antibody level $\geq$ 10 mIU/mL was considered protective. A seroprotection rate $\geq$90% one month after the third dose of hepatitis B vaccine was considered clinically acceptable. In addition, GMTs were calculated for each group.
- Analyses were performed for the intent-to-treat (ITT) and per-protocol (PP) populations, defined as:
  - ITT - subjects enrolled, vaccinated, and had least one post-vaccination safety or immunogenicity evaluation.
  - PP - included in the ITT population and did not violate the protocol with respect to vaccination or blood sample visits.

Surveillance:

Safety: Methods were similar to those in Study TC9704, except that in this study, all subjects were provided with "participant observation records" to record solicited local and systemic adverse events on a daily basis, on the evening of vaccination and for days 1-14 following vaccination.

Efficacy (Immunogenicity): Four blood samples were obtained from each subject in Group 1 (prior to immunization with TdcP, prior to the first dose of hepatitis B vaccine, prior to the second dose of hepatitis B vaccine, and one month following the third dose of hepatitis B vaccine). Three blood samples were obtained from each subject in Group 2 (prior to immunization with TdcP and the first dose of hepatitis B vaccine, prior to the second dose of hepatitis B vaccine, and one month following the third

dose of hepatitis B vaccine). Serum samples were tested for antibodies to tetanus toxin using an ELISA, for antibodies to diphtheria toxin using a ---------- assay, and for antibodies to hepatitis B surface antigen by ----------.

9.3.5 Results

9.3.5.1 Study Population

Table 39. Study TD9805 Characteristics of Study Population

	Group 1 (N=136)	Group 2 (N=136)
Age (years) mean range	 11.4 11.0-11.8	 11.3 11.0-11.8
Gender female male	 62 (45.6%) 74 (54.4%)	 63 (46.3%) 73 (53.7%)

Source: STN:103171/0.5000, Volume 4, page 48

9.3.5.2 Immunogenicity

Pre-immunization seroprotection levels for diphtheria were not reported in the BLA for the per-protocol population. In the intent to treat population, 100% of subjects in Groups 1 and 2 had a pre-vaccination diphtheria antitoxin level ≥0.01 IU/ml; 85.9% of subjects in Group 1 and 79.5% of subjects in Group 2 had a pre-vaccination diphtheria antitoxin level ≥0.1 IU/ml; 20.7% of subjects in Group 1 and 18.2% of subjects in Group 2 had a pre-vaccination diphtheria antitoxin level ≥1.0 IU/ml. Post-vaccination seroprotection rates for diphtheria were similar in the intent to treat and per protocol populations.

Table 40. Study TD9805 Proportion of subjects with specified levels of diphtheria and tetanus antibody, pre- and 1-month post-immunization, by study group, per protocol population

		≥ 0.01 IU/ml	**≥ 0. 1 IU/ml**	**≥ 1.0 IU/ml**	**≥4-fold rise**
Diphtheria	Timing	n %	n %	n %	%
Group 1[1] N=118	pre post	n/a 118(100.0)	n/a 118 (100.0)	n/a 118 (100.0)	 93.3[3]
Group 2[2] N=129	pre post	n/a 129 (100.0)	n/a 129 (100.0)	n/a 123 (95.3)	 93.9[3]
		≥ 0.01 IU/ml	**≥ 0.1 IU/ml**	**≥ 1.0 IU/ml**	**≥4-fold rise**
Tetanus		n %	n %	n %	
Group 1[1] N=118	pre post	118 (100.0) 118 (100.0)	118 (100.0) 118 (100.0)	60 (50.8) 118 (100.0)	 96.6
Group 2[2] N=129	pre post	128 (99.2) 129 (100.0)	127 (98.4) 129 (100.0)	59 (45.7) 129 (100.0)	 97.7

[1] Study group 1 received TdcP and hepatitis B vaccine separately, one month apart.
[2] Study group 2 received TdcP and hepatitis B vaccine concurrently, at separate sites.
[3]Data are from the intent to treat population: 135 subjects in group 1; and 134 subjects in group 2
n/a: data not provided for per-protocol population; see text above for data from intent to treat population.

Source: STN:103171/0.5000, Volume 1 page 46, and Volume 4, page 56; STN 103171/5.020 page 7

Table 41. Study TD9805 Tetanus and Diphtheria GMTs pre- and one month post-immunization, by study group, per protocol population

	Group 1[1] (N=118)	**Group 2[2] (N=129)**	**Group 2 vs. Group 1**	
	GMT	GMT	GMT ratio	90% CI
Diphtheria				
Pre	0.39	0.29	0.74	0.57, 0.97
Post	8.41	6.84	0.81	0.66, 1.00
Tetanus				
Pre	0.99	0.77	0.77	0.65, 0.92
Post	23.73	21.62	0.91	0.77, 1.07

[1] Study group 1 received TdcP and hepatitis B vaccine separately, one month apart.
[2] Study group 2 received TdcP and hepatitis B vaccine concurrently, at separate sites.
Source: STN:103171/0.5000, Volume 4, page 59 and STN 103171/0.5020 page 7

Table 42. Study TD9805 Hepatitis b seroprotection rates, post third vaccination, per protocol

	Group 1[1] (N=118)	Group 2[2] (N=129)
anti-HbSAg ≥ 10.0 mIU/ml	118 (100.0)	128 (99.2)

[1] Study group 1 received TdcP and hepatitis B vaccine separately, one month apart.
[2] Study group 2 received TdcP and hepatitis B vaccine concurrently, at separate sites.
Source: STN:103171/0.5000, Volume 4, page 139

Table 43. Study TD9805 GMTs for anti-Hepatitis B Surface Antigen, per protocol population

Group 1[1] (N=112)			**Group 2[2] (N=121)**			
	GMT	**90% CI**	**GMT**	**90% CI**	**GMT Ratio**	**90% CI**
Pre	0.33	(0.29, 0.39)	0.32	(0.29, 0.34)	1.05	(0.92, 1.21)
Post-dose 3	5582	(4194, 7429)	3431	(2542, 4632)	1.63	(1.15, 2.30)

[1] Study group 1 received TdcP and hepatitis B vaccine separately, one month apart.
[2] Study group 2 received TdcP and hepatitis B vaccine concurrently, at separate sites.
Source: STN:103171/0.5000, Volume 4, page 140

9.3.5.3 Safety: Frequencies of local and systemic adverse events that occurred during the first 72 hours following vaccination are presented in the table below.

Table 44. Study TD9805 Frequency of selected local and systemic adverse events that occurred during the first 72 hours following vaccination with TdcP, intent to treat population

Adverse Event	Severity	Study Group[1]	N	n	%	LCL	UCL
Redness	Any	1	135	22	16.30	10.50	23.63
		2	134	29	21.64	15.00	29.58
	≥ 35 mm	1	135	8	5.93	2.59	11.34
		2	134	11	8.21	4.17	14.21
	≥ 50 mm	1	135	7	5.19	2.11	10.39
		2	134	9	6.72	3.12	12.37
	≥ 100 mm	1	135	0	0.00	0.00	2.70
		2	134	0	0.00	0.00	2.72
Swelling	Any	1	135	27	20.00	13.61	27.75
		2	134	35	26.12	18.92	34.41
	≥ 35 mm	1	135	21	15.56	9.89	22.79
		2	134	23	17.16	11.20	24.63
	≥ 50 mm	1	135	20	14.81	9.29	21.95
		2	134	15	11.19	6.40	17.79
	≥ 100 mm	1	135	2	1.48	0.18	5.25
		2	134	1	0.75	0.02	4.09
Pain	Any	1	135	98	72.59	64.25	79.91
		2	134	107	79.85	72.05	86.28
	Moderate[2] or Worse	1	135	36	26.67	19.43	34.96
		2	134	49	36.57	28.42	45.32
	Severe[3]	1	135	3	2.22	0.46	6.36
		2	134	6	4.48	1.66	9.49
Fever	≥38.0°C	1	135	2	1.48	0.18	5.25
		2	134	4	2.99	0.82	7.47
	≥39.0°C	1	135	0	0.00	0.00	2.70
		2	134	1	0.75	0.02	4.09
	>40.0°C	1	135	0	0.00	0.00	2.70
		2	134	1	0.75	0.02	4.09
Chills	Any	1	135	18	13.33	8.1	20.25
		2	134	21	15.67	9.97	22.95

Adverse Event	Severity	Study Group[1]	N	n	%	LCL	UCL
	Moderate[2] or Worse	1	135	0	0.00	0.00	2.70
		2	134	6	4.48	1.66	9.49
	Severe[3]	1	135	0	0.00	0.00	2.70
		2	134	1	0.75	0.02	4.09
Joint pain	Any	1	135	28	20.74	14.25	28.56
		2	134	20	14.93	9.36	22.11
	Moderate[2] or Worse	1	135	8	5.93	2.59	11.34
		2	134	5	3.73	1.22	8.49
	Severe[3]	1	135	2	1.48	0.18	5.25
		2	134	1	0.75	0.02	4.09

[1] Group 1 received TdcP and hepatitis B vaccine separately, one month apart. Group 2 received TdcP and hepatitis B vaccine concurrently, at separate sites. For Group 2, local adverse events reflect those at the TdcP site.
[2] moderate = interfered with activities, but did not require medical care or absenteeism
[3] severe = incapacitating, unable to perform usual activities, required medical care or absenteeism
N indicates total number of subjects
n indicates number of subjects with specified adverse event
LCL indicates lower bound of 95% confidence interval
UCL indicates upper bound of 95% confidence interval
Source: STN:103171/0.5005, Volume 2, pages 67-69

Serious Adverse Events: Five months post-vaccination, one subject underwent surgery for a fractured elbow following a fall. Ten weeks post-vaccination, one subject was hospitalized for a fractured ankle.

9.3.6 Reviewer's Comments and Conclusions on Study TD9805

1. The age range of adolescents enrolled in this study was narrow (11-11.8 years).

2. High pre-immunization levels of antibodies to tetanus and diphtheria toxins were observed in the study population. Prior to vaccination, >98% of subjects had a tetanus antitoxin level ≥0.1 IU/ml, and > 80% had a diphtheria antitoxin level ≥0.1 IU/ml. Thus, it was more informative to assess the proportion of subjects with levels ≥1.0 IU/ml. Prior to vaccination, approximately 50% of subjects had a tetanus antitoxin level ≥1.0 IU/ml, and all achieved this level post-vaccination. Prior to vaccination, approximately 20% of subjects had a diphtheria antitoxin level ≥1.0 EU/ml, and more than 95% in each study group achieved this level post-vaccination.

3. For each study group, the booster response rate for tetanus was at least 97%, and approximately 93% for diphtheria. There was a trend towards lower post-vaccination GMTs for both tetanus and diphtheria antitoxins in the group that received concurrent hepatitis B vaccination. This difference may reflect, in part, slightly lower pre-immunization levels in Group 2, and is unlikely clinically relevant in view of the high levels of seroprotection.

4. Over 99% of subjects in both groups achieved seroprotective levels (≥10 mIU/ml) for hepatitis B antibody: 100% in Group 1 and 99.2% in Group 2. As observed for tetanus and diphtheria, concurrent immunization was associated with a lower post-vaccination GMT for hepatitis B antibody, although the clinical relevance of this finding is not known.

5. Overall, rates of local and systemic adverse events were comparable between the two study groups. Concurrent immunization with hepatitis B vaccine did not appear to negatively affect the safety profile of TdcP. The reported frequencies of adverse events were generally consistent with those reported following Td or TdcP in Studies TC9704 and TD9707.

9.4 TD9809 Safety and Immunogenicity of TdcP-IPV Compared to TdcP-IPV and Hepatitis B Vaccine Given Concurrently in Adolescents 11-14 Years of Age

9.4.1 Study Period January 1999 – June 2000

9.4.2 Objectives
Primary: Determine the safety and immunogenicity of TdcP-IPV compared to TdcP-IPV and hepatitis B vaccine administered concurrently in adolescents 11-14 years of age.
Secondary: Determine whether concurrent administration of TdcP-IPV and hepatitis B vaccines at 11-14 years of age results in detectable immunologic interactions between components of the two vaccines.

9.4.3 Design: Phase II, open label, two groups, randomized, controlled clinical trial.

Study Groups: Subjects in Group1 received TdcP-IPV and the first dose of hepatitis B vaccine separately, one month apart. Subjects in Group 2 received TdcP-IPV and the first dose of hepatitis B vaccine concurrently at separate administration sites.

Vaccines: The TdcP-IPV formulation was the same as that used in Study TD9707. Hepatitis B Vaccine (Recombivax HB®) manufactured by Merck, contains 5 µg of HBsAg per 0.5 ml dose, thimerosal (1:20,000) as a preservative, aluminum hydroxide as an adjuvant.

9.4.4 Protocol
Population: The study was conducted at one study center in Canada. Inclusion and exclusion criteria were essentially the same as those used in Study TD9805. In addition, prior receipt of any polio vaccine within the past 5 years was an exclusion criterion.

Vaccination schedule: Subjects in Group 1 were immunized with TdcP-IPV, followed by hepatitis B immunization one month later. Subjects in Group 2 were immunized with TdcP-IPV and the first dose of hepatitis B vaccine, concurrently, at separate sites. For both groups, the second and third dose of hepatitis B vaccine were given 1 month and 6 months, respectively, after the initial hepatitis B vaccination. Vaccines were injected intramuscularly into the deltoid.

Endpoints/statistical considerations
- The sample size was based on an evaluation of immune response to the pertussis antigens.
- The primary safety evaluation involved an observational comparison of solicited local and systemic adverse events between the recipients of TdcP-IPV vaccine and the recipients of TdcP-IPV + hepatitis B vaccine given concurrently. For each adverse event, the difference between groups and two-sided 90% confidence interval on the difference was calculated. The adverse event rates in the two groups were considered clinically equivalent if the difference in the rates was within 15% (based on lower and upper bounds of the 90% confidence interval on the difference).
- The primary immunogenicity evaluation included a comparison of the proportion of subjects in each vaccine group with one month post-immunization levels of antibodies to tetanus and diphtheria toxins $\geq$0.01 IU/ml, $\geq$0.1 IU/ml, and $\geq$1.0 IU/ml. For tetanus and diphtheria, seroprotection was defined as an antibody level $\geq$0.1 IU/ml. Differences in seroprotection rates and two-sided 90% confidence intervals on the differences were calculated. For each antigen (diphtheria and tetanus), a

seroprotection rate of ≥95% was considered clinically acceptable. For comparing seroprotection rates between the two groups, they were considered clinically equivalent if the difference was within 10% (based on lower and upper bounds of the 90% confidence interval on the difference). Pertussis and poliovirus antibody responses were also analyzed.

- The evaluation of the immune response to hepatitis B vaccine was considered a secondary analysis. A hepatitis B surface antigen antibody level ≥10 mIU/mL was considered indicative of protection.
- As secondary analyses, for each serological outcome, the pre-vaccination and post-vaccination GMTs with 95% confidence intervals were calculated for each study group. Pre- and post-vaccination GMT ratios of Group 1 and Group 2 were calculated with two-sided 90% confidence intervals on the ratios.
- Analyses were performed for intent-to-treat (ITT) and per-protocol (PP) populations, defined as:
  - ITT - enrolled, received TdcP-IPV, and had at least one post-vaccination safety or immunogenicity evaluation.
  - PP - in ITT population and did not violate protocol with respect to vaccination or blood samples.

Surveillance:
Safety: Methods were similar to those in Study TD9805. One notable difference was that in Study TD9809, monitoring for solicited adverse events included the use of individual subject diaries, in addition to follow-up telephone calls.
Efficacy (Immunogenicity): The methods were essentially the same as in Study TD9805.

9.4.5 Results

9.4.5.1 Study Population

Table 45. Study TD9809 Characteristics of Study Population

	Group 1[1] (N=144)	Group 2[2] (N=132)
Age (years)		
mean	12.4	12.4
range	11.0-13.9	11.0-14.0
Gender		
female	75 (52.1%)	59 (44.7%)
male	69 (47.9%)	73 (55.3%)

Source: STN:103171/0.5000, Volume 5, page 204
[1] Study group 1 received TdcP-IPV and hepatitis B vaccine separately, one month apart.
[2] Study group 2 received TdcP-IPV and hepatitis B vaccine concurrently, at separate sites.

9.4.5.2 Immunogenicity Results were similar for the per protocol and intent to treat study populations. For the per protocol analyses, pre-immunization seroprotection rates for diphtheria were not provided.

Table 46. Study TD9809 Proportion of subjects with specified levels of diphtheria antibody, pre- and 1-month post-immunization, by study group, intent to treat population

	Group 1[1] N=144	Group 2[2] N=132	Difference (Group 2-Group 1)
	n %	n %	% (90% CI)
Pre			
≥ 0.01 IU/ml	138 (95.8)	132 (100.0)	4.2 (1.4, 6.9)
≥ 0. 1 IU/ml	91 (63.2)	89 (67.4)	4.2 (-5.2, 13.6)
≥ 1.0 IU/ml	14 (9.7)	13 (9.8)	0.1 (-5.8, 6.0)
Post			
≥ 0.01 IU/ml	142 (100.0)	132 (100.0)	0.0
≥ 0. 1 IU/ml	140 (98.6)	132 (100.0)	1.4 (-0.2, 3.0)
≥ 1.0 IU/ml	117 (82.4)	117 (88.6)	6.2 (-0.7, 13.2)

[1] Study group 1 received TdcP-IPV and hepatitis B vaccine separately, one month apart.
[2] Study group 2 received TdcP-IPV and hepatitis B vaccine concurrently, at separate sites.
Source: STN:103171/0.5000, Volume 5, page 211, and volume 6, page 5

Table 47. Study TD9809 Proportion of subjects with specified levels of tetanus antibody, pre- and 1-month post-immunization, by study group, per protocol population

	Group 1[1] N=118		Group 2[2] N=123		Difference (Group 2-Group 1)	
	n	%	n	%	Diff %	90% CI
Pre						
≥ 0.01 IU/ml	118	100.0	123	100.0	.	
≥ 0. 1 IU/ml	118	100.0	122	99.2	-0.8	-2.1, 0.5
≥ 1.0 IU/ml	44	37.3	46	37.4	0.1	-10.1, 10.4
Post						
≥ 0.01 IU/ml	118	100.0	123	100.0	.	
≥ 0. 1 IU/ml	118	100.0	123	100.0	.	
≥ 1.0 IU/ml	117	99.2	122	99.2	0.0	-1.9, 2.0

[1] Study group 1 received TdcP-IPV and hepatitis B vaccine separately, one month apart.
[2] Study group 2 received TdcP-IPV and hepatitis B vaccine concurrently, at separate sites.
Source: STN:103171/0.5020 page 8

Table 48. Study TD9809 Tetanus and Diphtheria GMTs pre- and one month post-immunization, by study group, per protocol population

	Group 1[1] (N=118)	Group 2[2] (n=123)	Group 2 vs. Group 1	
	GMT	GMT	GMT ratio	90% CI
Diphtheria				
Pre	0.16	0.20	1.26	0.94, 1.69
Post	2.79	3.00	1.07	0.85, 1.35
Tetanus				
Pre	0.74	0.72	0.98	0.81, 1.18
Post	16.83	14.81	0.88	0.72, 1.07

[1] Study group 1 received TdcP-IPV and hepatitis B vaccine separately, one month apart.
[2] Study group 2 received TdcP-IPV and hepatitis B vaccine concurrently, at separate sites.
Source: STN:103171/0.5000, Volume 5, page 215 and STN 103171/0.5020 page 8

Table 49. Study TD9809 Distribution of post-third dose anti-HBsAg titers, by study group, intent to treat population

anti-HbSAg (mIU/ml)	Group 1[1] (N=140) n (%)	Group 2[2] (N=128) n (%)
≤ 10.0	0 (0.0)	0 (0.0)
10-100	1 (0.7)	4 (3.1)
100-1,000	26 (18.6)	20 (15.6)
>1,000	113 (80.7)	104 (81.2)
≥ 10	140 (100.0)	128 (100.0)

[1] Study group 1 received TdcP-IPV and hepatitis B vaccine separately, one month apart.
[2] Study group 2 received TdcP-IPV and hepatitis B vaccine concurrently, at separate sites.
Source: STN:103171/0.5000, Volume 5, page 215

Table 50. Study TD9809 GMTs for anti-HBsAg, by study group, intent to treat population

Group 1[1] (N=143)			**Group 2[2] (N=132)**			
	GMT	**90% CI**	**GMT**	**90% CI**	**GMT Ratio**	**90% CI**
Pre	0.32	(0.30, 0.35)	0.31	(0.29, 0.34)	1.02	(0.93, 1.13)
Post-dose 3	3053	(2425, 3844)	3621	(2754, 4761)	0.84	(0.63, 1.14)

[1] Study group 1 received TdcP and hepatitis B vaccine separately, one month apart.
[2] Study group 2 received TdcP and hepatitis B vaccine concurrently, at separate sites.
Source: STN:103171/0.5000, Volume 5, page 216 and Volume 6, page 16

9.4.5.3 Safety The frequency of local and systemic adverse events that occurred during the first 72 hours following TdcP-IPV vaccination are provided in the table below.

Table 51. Study TD9809. Frequency of selected local and systemic adverse events that occurred during the first 72 hours following TdcP-IPV, Intent-to-Treat Population

Adverse Event	Severity	Study Group[1]	N	N	%	LCL	UCL
Redness	Any	1	144	39	27.08	20.02	35.11
		2	132	34	25.76	18.54	34.09
	≥ 35 mm	1	144	5	3.47	1.14	7.92
		2	132	12	9.09	4.79	15.34
	≥ 50 mm	1	144	4	2.78	0.76	6.96
		2	132	10	7.58	3.69	13.49
	≥ 100 mm	1	144	0	0.00	0.00	2.53
		2	132	0	0.00	0.00	2.76
Swelling	Any	1	144	34	23.61	16.94	31.40
		2	132	29	21.97	15.23	30.00
	≥ 35 mm	1	144	20	13.89	8.69	20.63
		2	132	20	15.15	9.51	22.43
	≥ 50 mm	1	144	13	9.03	4.89	14.94
		2	132	14	10.61	5.92	17.15
	≥ 100 mm	1	144	0	0.00	0.00	2.53
		2	132	1	0.76	0.02	4.15
Pain	Any	1	144	138	95.83	91.15	98.46
		2	132	126	95.45	90.37	98.31
	Moderate[2] or Worse	1	144	57	39.58	31.54	48.06
		2	132	54	40.91	32.43	49.8
	Severe[3]	1	144	1	0.69	0.02	3.81
		2	132	0	0.00	0.00	2.76
Fever[4]	≥38.0 °C	1	144	7	4.86	1.98	9.76
		2	132	5	3.79	1.24	8.62
	≥39.0 °C	1	144	0	0.00	0.00	2.53
		2	132	1	0.76	0.02	4.15
	≥40 °C	1	144	0	0.00	0.00	2.53
		2	132	0	0.00	0.00	2.76
Chills	Any	1	144	29	20.14	13.92	27.63
		2	132	26	19.70	13.29	27.51

Adverse Event	Severity	Study Group[1]	N	n	%	LCL	UCL
	Moderate[2] or Worse	1	144	6	4.17	1.54	8.85
		2	132	3	2.27	0.47	6.50
	Severe[3]	1	144	1	0.69	0.02	3.81
		2	132	0	0.00	0.00	2.76
Joint pain	Any	1	144	29	20.14	13.92	27.63
		2	132	31	23.48	16.55	31.65
	Moderate[2] or Worse	1	144	10	6.94	3.38	12.40
		2	132	6	4.55	1.69	9.63
	Severe[3]	1	144	1	0.69	0.02	3.81
		2	132	0	0.00	0.00	2.76

[1]Group 1 - Subjects received TdcP-IPV at Month 0 and Hepatitis B vaccine at Months 1, 2, and 7; Group 2 - Subjects received TdcP-IPV and Hepatitis B vaccines concurrently at separate sites at Month 0 and Hepatitis B vaccine at Months 1 and 6. For Group 2, local adverse events reflect those that occurred at the TdcP site.
[2] moderate = interfered with activities, but did not require medical care or absenteeism
[3] severe = incapacitating, unable to perform usual activities, required medical care or absenteeism
[4] Fever - Moderate (39.0-39.9 ^{o}C), Severe (Over 40 ^{o}C)
N indicates total number of subjects
n indicates number of subjects with specified adverse event
LCL indicates lower bound of 95% confidence interval
UCL indicates upper bound of 95% confidence interval
Source: STN:103171/0.5005, Volume 2, pages 71-73

Serious Adverse Events: A serious adverse event was reported in three subjects from Group 2 (leg fracture playing sports, seven days after the third dose of Hepatitis B vaccine; diabetic hospitalized with viral gastroenteritis and unstable blood glucose, three months after the second dose of Hepatitis B vaccine; appendicitis 11 days after the first dose of Hepatitis B and TdcP-IPV vaccines), and in one subject from Group 1 (leg fracture playing sports, 29 days after the third dose of Hepatitis B vaccine).

9.4.6 Reviewer's Comments and Conclusions on Study TD9809

1. High pre-immunization levels of antibodies, particularly to tetanus, were observed in the study population. Prior to vaccination, >99% of subjects had a tetanus antitoxin level $\geq$0.1 IU/ml, and approximately 65% had a diphtheria antitoxin level $\geq$0.1 IU/ml. After vaccination, approximately 99% of subjects achieved a diphtheria antitoxin level $\geq$0.1 IU/ml. Prior to vaccination, approximately 37% of subjects had a tetanus antitoxin level $\geq$1.0 IU/ml, and approximately 99% achieved this level post-vaccination. Prior to vaccination, approximately 10% of subjects had a diphtheria antitoxin level $\geq$1.0 IU/ml, and approximately 85% of subjects in each study group achieved this level post-vaccination.

2. The analysis of GMTs pre- and post immunization suggested a robust booster response, overall, to both tetanus and diphtheria whether TdcP-IPV was given separately from or concurrently with hepatitis B vaccine.

3. All subjects in both groups achieved a seroprotective level ($\geq$10 mIU/ml) for hepatitis B antibody after the third dose. Post-third dose GMTs for anti-HBsAg were similar in the two groups.

4. Overall, responses to tetanus and diphtheria toxoids in TdcP-IPV and hepatitis B vaccine did not appear to be adversely affected by simultaneous vaccination in this study.

5. Overall, rates of local and systemic adverse events were comparable between the two study groups. Concurrent immunization with hepatitis B vaccine did not appear to negatively affect the safety of TdcP.

9.5 Td Clinical Trial in the Canadian Armed Forces (historical lot consistency study)

9.5.1 Study Period: Dates not provided. One page of the study report is dated November 1978.

9.5.2 Objective: Examine antibody responses and reactogenicity of Td.

9.5.3 Design: Three-armed, open, non-controlled clinical trial, using three Td lots (11043-1, 11044-1, 11045-1) containing 5 Lf of tetanus toxoid, 2 Lf of diphtheria toxoid, 1.5 mg of aluminum phosphate, and 0.1% thimerosal per 0.5 ml dose. Lot 11044-1 was administered only to male subjects because no female subjects were available at the time this lot was administered.

9.5.4 Protocol
Population: Male and female Canadian Armed Forces recruits at Cornwallis CFB. There were no other specified inclusion or exclusion criteria. It was anticipated that most subjects would have been previously immunized against tetanus and diphtheria. Information on immunization histories was not collected.
Vaccination Schedule: Two doses, four weeks apart.
Concomitant Vaccines: At the time of the first dose of Td, subjects received meningococcal vaccine, oral poliovirus vaccine and tuberculin PPD. At the time of the second dose of Td, subjects also received yellow fever vaccine. No further information was provided about concomitantly administered products.
Endpoints:
- Local and general adverse events
- Tetanus antitoxin levels, measured by mouse neutralization test
- Diphtheria antitoxin levels, measured by rabbit skin neutralization test

Surveillance:
- Safety: Information on adverse events was collected for four or more days following each dose via daily telephone calls or home visits. Information was solicited on injection site discomfort, pain, swelling, redness, induration, and lymphadenopathy, fever, chills, headache, malaise, muscle ache, nausea, abdominal pain, and joint pain. Individual subject diary cards were not used.
- Efficacy (Immunogenicity): Three blood samples were obtained--immediately prior to the first dose of Td, and at four and eight weeks after the first dose. Tetanus antitoxin levels were measured by the mouse neutralization test. Diphtheria antitoxin levels were measured by the rabbit skin neutralization test.

Reporting of immunogenicity data: For the tetanus and diphtheria antitoxin assays, four five-fold dilutions of each serum sample were mixed with equal volumes of challenge toxin, and injected into animals. The result for each serum sample was reported as a range. The lower value of the range was the dilution that did not induce the outcome effect in the animals (e.g., paralysis or death in mice for tetanus antitoxin assay). The upper value of the range was the dilution at which the outcome effect was observed. For each subject, the diphtheria and tetanus antitoxin levels were converted to mean titers based on the geometric mean of the upper and lower level of the range. Overall GMTs were computed across all subjects. The tetanus and diphtheria antitoxin assays were performed using U.S. reference antitoxin standards.
Statistical analysis plan: The study protocol did not include a statistical analysis plan or any pre-specified criteria for demonstrating lot consistency. The statistical analyses of lot-to-lot comparisons

presented in this review were not specified in the study protocol. These analyses were requested by CBER in the December 2001 complete response letter.

9.5.5 Results

9.5.5.1 Population

Table 50. Canadian Armed Forces Study: Age and sex of subjects

	N=347
	n (%)
Age (years)	
17-19	168 (48.4)
20-24	162 (46.7)
25-29	15 (4.3)
Sex	
male	260 (74.9)
female	87 (25.1)

source: STN:103171/0.5000, Volume 1, page 24

9.5.5.2 Immunogenicity

Table 51. Canadian Armed Forces Study: Range equivalencies for tetanus and diphtheria antibody titer point values

Value (units/ml)	Mean Titer Range (units/ml)
<0.01	<0.01
0.02	0.01-0.04
0.11	0.05-0.24
0.56	0.25-1.24
2.80	1.25-6.24
14.0	6.25-31.24
70.0	31.25-156.25

Source: STN:103171/0.5000, Volume 1, page 26

Results of the immunogenicity analyses for tetanus and diphtheria are presented in the tables below.

Table 52. Canadian Armed Forces Study: Tetanus antitoxin GMTs pre-vaccination and four weeks following the first (booster) dose of Td in adults 17-29 years of age, by Td lot.

	pre GMT	post GMT
Lot		
11043-1 (n=113)	1.12	4.17
11044-1 (n=93)	0.71	4.46
11045-1 (n=92)	0.73	3.00

Source: PLA 86-0205, pages 87, 89, 91

Table 53. Canadian Armed Forces Study: Diphtheria antitoxin GMTs pre-vaccination and four weeks following the first (booster) dose of Td in adults 17-29 years of age, by Td lot.

	pre GMT	post GMT
Lot		
11043-1 (n=112)	0.17	1.13
11044-1 (n=93)	0.12	1.26
11045-1 (n=92)	0.14	0.97

Source: PLA 86-0205, pages 94, 96, 98

Table 54. Canadian Armed Forces Study: Analysis of pre- and post-dose 1 (booster) GMT ratios (lot comparisons) for tetanus and diphtheria antitoxin levels

			Pre					Post				
Antigen	Lot	vs Lot	N	M	GMT Ratio	LCL	UCL	N	M	GMT Ratio	LCL	UCL
Tetanus	11043-1	11044-1	124	105	1.52	1.09	2.10	113	95	0.94	0.73	1.22
	11043-1	11045-1	124	103	1.60	1.15	2.21	113	93	1.39	1.08	1.80
	11044-1	11045-1	105	103	1.05	0.75	1.48	95	93	1.48	1.13	1.93
Diphtheria	11043-1	11044-1	124	105	1.44	0.93	2.25	112	95	0.90	0.65	1.23
	11043-1	11045-1	124	103	1.39	0.89	2.17	112	93	1.18	0.85	1.62
	11044-1	11045-1	105	103	0.96	0.60	1.53	95	93	1.31	0.94	1.84

Values below the LOQ were replaced with 1/2 the LOQ.
N, M - Sample sizes (missing observations not included) for groups involved in comparison
GMTs Ratio - Ratio of GMTs for two groups
LCL, UCL - Lower and upper limits of the two-sided 90% confidence interval for the ratio of GMTs for two groups
Source: STN 103171/0.5005, Volume 2, page 197

Table 55. Canadian Armed Forces Study: Lot-to-lot comparison of pre- and post-dose 1 (booster) seroprotection rates for diphtheria (antitoxin level ≥ 0.1 IU/ml)

						Between Lot Comparison			
						vs 11044-1		vs 11045-1	
Time Point	Lot	N	n	%	(95 % CI)	Difference (%)	(95 % CI)	Difference (%)	(95 % CI)
Pre-Vaccination	11043-1	124	91	73.4	(64.7, 80.9)	2.91	(-8.8, 14.6)	7.37	(-4.6, 19.4)
	11044-1	105	74	70.5	(60.8, 79.0)			4.46	(-8.2, 17.1)
	11045-1	103	68	66.0	(56.0, 75.1)				
Post-Vaccination	11043-1	112	112	100.0	(96.8, 100.0)	4.21	(0.2, 8.2)	5.38	(0.8, 10.0)
	11044-1	95	91	95.8	(89.6, 98.8)			1.17	(-4.9, 7.3)
	11045-1	93	88	94.6	(87.9, 98.2)				

Values below the LOQ were replaced with 1/2 the LOQ.
N-Number of subjects who provided a measurement. n-Number of subjects attaining the specified titre.
Source: STN 103171/0.5005, Volume 2, page 200

For each lot of Td, >94% of subjects had a pre-vaccination tetanus antitoxin level ≥0.1 IU/ml. At lot-to-lot comparative analysis of the proportion of subjects with tetanus antitoxin levels ≥1.0 IU/ml pre- and post-vaccination are presented in the table below.

Table 56. Canadian Armed Forces Study: Lot-to-lot comparison of the proportion of subjects with pre- and post-dose 1 (booster) tetanus antitoxin level ≥ 1.0 IU/ml

						Between Lot Comparison			
						vs 11044-1		vs 11045-1	
Time Point	Lot	N	n	%	(95 % CI)	Difference %	(95 % CI)	Difference %	(95 % CI)
Pre-Vaccination	11043-1	124	59	47.6	(38.5, 56.7)	9.49	(-3.3, 22.3)	9.72	(-3.1, 22.6)
	11044-1	105	40	38.1	(28.8, 48.1)			0.23	(-13.0, 13.4)
	11045-1	103	39	37.9	(28.5, 48.0)				
Post-Vaccination	11043-1	113	104	92.0	(85.4, 96.3)	-4.81	(-10.9, 1.3)	6.01	(-2.6, 14.7)
	11044-1	95	92	96.8	(91.0, 99.3)			10.82	(2.9, 18.7)
	11045-1	93	80	86.0	(77.3, 92.3)				

Values below the LOQ were replaced with 1/2 the LOQ.
N-Number of subjects who provided a measurement. n-Number of subjects attaining the specified titre level.
Source: STN 103171/0.5005, Volume 2, page 201

Table 57. Canadian Armed Forces Study: Lot-to-lot comparison of percent of subjects with a booster response[1] to tetanus toxoid following Td

					Between Lot Comparison			
					vs 11044-1		vs 11045-1	
Lot	N	n	%	(95 % CI)	Difference (%)	(95 % CI)	Difference (%)	(95 % CI)
11043-1	113	64	56.6	(47.0, 65.9)	-7.88	(-21.2, 5.5)	-0.97	(-14.6, 12.6)
11044-1	93	60	64.5	(53.9, 74.2)			6.91	(-7.1, 20.9)
11045-1	92	53	57.6	(46.9, 67.9)				

[1] Booster response was evaluated following the first dose of Td in the study. Booster response is defined as a ≥ 4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 units/ml must also have a post-vaccination level ≥ 0.1 units/ml to be considered a responder.
Note: Values below the LOQ were replaced with 1/2 the LOQ.
N-Number of subjects who provided a measurement. n-Number of subjects attaining a 4-fold increase.
Source: STN 103171/0.5005, Volume 2, page 204

Table 58. Canadian Armed Forces Study: Lot-to-lot comparison of percent of subjects with a booster response[1] to diphtheria toxoid following Td

					Between Lot Comparison			
					vs 11044-1		vs 11045-1	
Lot	N	n	%	(95 % CI)	Difference (%)	(95 % CI)	Difference (%)	(95 % CI)
11043-1	112	73	65.2	(55.6, 73.9)	-12.24	(-24.5, 0.0)	-3.30	(-16.3, 9.7)
11044-1	93	72	77.4	(67.6, 85.4)			8.94	(-3.8, 21.7)
11045-1	92	63	68.5	(58.0, 77.8)				

[1] Booster response was evaluated following the first dose of Td in the study. Booster response is defined as a ≥ 4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 units/ml must also have a post-vaccination level ≥ 0.1 units/ml to be considered a responder.
Note: Values below the LOQ were replaced with 1/2 the LOQ.
N-Number of subjects who provided a measurement. n-Number of subjects attaining a 4-fold increase.
Source: STN 103171/0.5005, Volume 2, page 205

9.5.5.3 Safety Results following the first dose of Td are presented in the table below. The frequencies of local adverse events after the second dose were generally similar to those following the first dose. The frequencies of most systemic adverse events tended to be somewhat lower following the second dose than following the first dose. Although data were not tabulated separately for males and females, the sponsor noted that for the two lots administered to both male and female subjects, local discomfort was reported more frequently in females than males (37% vs. 14%, and 45% vs. 12%, for each of the two lots, respectively). Based on descriptive data provided, there was no apparent consistent pattern of differences in frequency of adverse events between the three lots.

Table 59. Canadian Armed Forces Study: Local and systemic adverse events following the first dose (booster) of Td (pooled lots; N=346)

Adverse Event	Day 1 N (%)	Day 2 n (%)	Day 3 n (%)	Day 4 n (%)
Local				
Redness	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)
Swelling	4 (1.2)	3 (0.9)	3 (0.9)	2 (0.6)
Discomfort	66 (19.1)	55 (15.9)	14 (4.0)	7 (2.0)
Pain	8 (2.3)	9 (2.6)	5 (1.4)	4 (1.2)
Systemic				
Fever $\geq$38°C[1]	4 (1.2)	3 (0.9)	3 (0.9)	2 (0.6)
Chills	6 (1.7)	4 (1.2)	1 (0.3)	2 (0.6)
Headache	16 (4.6)	10 (2.9)	3 (0.9)	4 (1.2)
Malaise	11 (3.2)	5 (1.4)	1 (0.3)	4 (1.2)
Muscle ache	21 (6.1)	14 (4.0)	5 (1.4)	1 (0.3)
Joint pain	4 (1.2)	5 (1.4)	2 (0.6)	1 (0.3)

Source: STN:103171/0.5000, Volume 1, page 25

[1] includes cases assumed to be $\geq$38°C when fever was reported but temperature was not recorded

9.5.6 Reviewer's Comments and Conclusions on Study of Td in Canadian Armed Forces Recruits

1. From a clinical view, because of several limitations, this study does not seem adequate to support manufacturing consistency of Td. No information was provided on randomization or blinding, there were no pre-specified criteria to demonstrate lot consistency, and there was no pre-specified statistical analysis plan or evaluation of statistical power to assess any lot consistency endpoints. Criteria currently recommended by CBER for the evaluation of lot consistency of other vaccines that contain tetanus and diphtheria toxoids that are intended for use as booster vaccination [primary equivalence criterion: 90% CI for the ratio of lot GMTs not less than 0.67 and not greater than 1.5; secondary equivalence criterion: 95% CI for the difference in booster response rates not to exceed $\pm$10%), were not met for most comparisons. These criteria have been recommended for studies in which ELISA or in vitro neutralization assays are used for measuring tetanus and diphtheria antitoxin levels, and they may not be appropriate for the---------- assays that were used in this historical study. Wide confidence intervals for GMT ratios and differences in booster response rates may reflect, in part, variability associated with the assays, inadequate sample size, and/or imbalances in pre-vaccination GMTs among subjects who received different lots. The failure to meet the secondary equivalence criteria may also reflect, in part, the definition of booster response, which required a 4-fold increase in antibody level, even in subjects who had a high pre-vaccination level. The results of the lot-to-lot comparative analyses from this study are difficult to interpret, and in my opinion, do not support consistency of manufacturing for the candidate Td vaccine.

2. There is limited information on how adverse events were monitored in this study. Reported frequencies of local and systemic adverse events are much lower than those reported in more recent studies of Td or Td combination vaccines. This finding raises questions about how intensively adverse events were monitored and whether safety results obtained from the study population are generalizable to the U.S. population intended to receive this vaccine.

9.6 Td-Inactivated Poliomyelitis (Td-IPV) Vaccine Adsorbed (Historical study)

9.6.1 Study Period: October 1981-May 1982
9.6.2 Objective: Examine antibody responses and reactogenicity of Td-IPV in subjects who had received previous immunization against tetanus, diphtheria, and poliomyelitis.
9.6.3 Design: Three-armed, open, non-controlled clinical trial conducted at several high schools in two geographic areas. Three Td-IPV lots (18001-21, 18002-21, and 18003-21) containing 5 Lf of tetanus toxoid, 2 Lf of diphtheria toxoid, 1.5 mg of aluminum phosphate, and 0.375% 2-phenoxyethanol per 0.5 ml dose were used. The three Td-IPV lots were formulated from three different lots of tetanus concentrates and three different lots of diphtheria concentrates. Lot 18003-21 was administered to groups of participants in both study areas. The other two lots each were used in only one study area.
9.6.4 Protocol
Population: The study was conducted at several high schools in Perth County, Ontario (P sites) and in Corner Brook and Stephenville, Newfoundland (CB sites) during the period October 1981 through May 1982. The study population consisted of students ages 14-19 years who had been previously immunized against tetanus, diphtheria, and poliomyelitis. There were no other inclusion or exclusion criteria.
Vaccination schedule: 1 dose
Concomitant Vaccines: Not specified.
Endpoints:
- Local and general adverse events
- Tetanus antitoxin levels, measured by mouse toxin neutralization test
- Diphtheria antitoxin levels, measured by micro neutralization test using cell culture

Surveillance:
- Safety: Subjects were monitored immediately following immunization and for the three subsequent days with observations recorded on individual record forms. At the CB sites, subjects reportedly were monitored for safety in an informal group setting. At the P sites, subjects were monitored individually with each subject recording oral temperatures and other solicited adverse events. At the time of post-vaccination blood sampling (7 and 28 days following vaccination), subjects were asked about clinical reactivity that had not been observed during the three-day monitoring period.
- Efficacy (Immunogenicity): Three blood samples were obtained (immediately prior to the first dose of Td, and at seven days and 28 days following vaccination). Tetanus antitoxin levels were determined by the mouse toxin neutralization test. Diphtheria antitoxin levels were determined by a micro neutralization test using cell culture.

Statistical plan: The study protocol did not include a statistical analysis plan or any pre-specified criteria for demonstrating lot consistency. The statistical analyses of lot-to-lot comparisons presented in this review were not specified in the study protocol. These analyses were requested by CBER in the December 2001 complete response letter.

9.6.5 Results

9.6.5.1 Population: A total of 276 subjects (122 males and 154 females) ages 14-19 years were enrolled, including 149 subjects at P sites and 127 subjects at CB sites.

9.6.5.2 Immunogenicity: Results of the immunogenicity analyses are presented in the tables below.

Table 60. Historical Td-IPV Study: Lot to lot comparison of percent of subjects with a booster response[1] to tetanus toxoid following Td-IPV

					Between Lot Comparison			
					vs 18002-21		vs 18003-21	
Lot	N	n	%	(95 % CI)	Difference (%)	(95 % CI)	Difference (%)	(95 % CI)
18001-21	75	47	62.7	(50.7, 73.6)	-1.2	(-16.2, 13.9)	-6.6	(-20.5, 7.2)
18002-21	83	53	63.9	(52.6, 74.1)			-5.4	(-18.8, 7.9)
18003-21	114	79	69.3	(60.0, 77.6)				

[1] Booster response is defined as a ≥ 4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 IU/ml must also have a post-vaccination level ≥ 0.1 IU/ml to be considered a responder.

Note:Values below the LOQ were replaced with 1/2 the LOQ.

N-Number of subjects who provided a measurement. n-Number of subjects attaining a 4-fold increase.

Source: STN:103171/0.5005, Volume 2, page 287

Table 61. Historical Td-IPV Study: Lot to lot comparison of percent of subjects with a booster response[1] to diphtheria toxoid following Td-IPV

					Between Lot Comparison			
					vs 18002-21		vs 18003-21	
Lot	N	n	%	(95 % CI)	Difference (%)	(95 % CI)	Difference (%)	(95 % CI)
18001-21	75	47	62.7	(50.7, 73.6)	-8.4	(-23.1, 6.2)	-9.3	(-23.0, 4.4)
18002-21	83	59	71.1	(60.1, 80.5)			-0.8	(-13.6, 11.9)
18003-21	114	82	71.9	(62.7, 79.9)				

[1] Seroresponse is defined as a ≥ 4-fold increase in post-vaccination antitoxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 IU/ml must also have a post-vaccination level ≥ 0.1 IU/ml to be considered a responder.

Note:Values below the LOQ were replaced with 1/2 the LOQ.

N-Number of subjects who provided a measurement. n-Number of subjects attaining a 4-fold increase.

Source: STN:103171/0.5005, Volume 2, page 288

Table 62. Historical Td-IPV Study: Tetanus and diphtheria antitoxin geometric mean titers pre-vaccination and 28 days following Td-IPV vaccination, by Td lot, and study center area.

			Tetanus		Diphtheria	
			pre GMT (IU/ml)	post GMT (IU/ml)	pre GMT (IU/ml)	post GMT (IU/ml)
Lot	Study Center	N				
18001	CB	76	0.67	2.68	0.16	1.22
18002	P	83	0.79	2.54	0.23	1.73
18003	CB	51	0.63	2.55	0.12	0.98
18003	P	64	0.79	3.52	0.17	1.37

Source: STN:103171/0.5000, Volume 1, page 34

Table 63. Historical Td-IPV Study: Lot-to-lot comparative analysis of GMTs for tetanus and diphtheria antitoxin

			Pre-Vaccination					28 Days Post Vaccination				
Antigen	Lot	vs Lot	N	M	GMT Ratio	LCL	UCL	N	M	GMT Ratio	LCL	UCL
Tetanus	18001-21	18002-21	76	83	0.85	0.62	1.16	75	83	1.06	0.90	1.23
	18001-21	18003-21	76	115	0.94	0.70	1.26	75	114	0.88	0.76	1.02
	18002-21	18003-21	83	115	1.11	0.83	1.47	83	114	0.83	0.72	0.96
Diphtheria	18001-21	18002-21	76	83	0.69	0.41	1.17	75	83	0.71	0.51	0.97
	18001-21	18003-21	76	115	1.10	0.68	1.80	75	114	1.03	0.76	1.38
	18002-21	18003-21	83	115	1.60	0.99	2.57	83	114	1.45	1.09	1.94

Values below the LOQ were replaced with 1/2 the LOQ.
N, M - Sample sizes (missing observations not included) for groups involved in comparison
GMTs Ratio - Ratio of GMTs for two groups
LCL, UCL - Lower and upper limits of the two-sided 90% confidence interval for the ratio of GMTs for two groups
Source: STN:103171/0.5005, Volume 2, page 294

Table 64. Historical Td-IPV Study: Comparative analysis of the proportion of subjects with a tetanus antitoxin level ≥1.0[1], by lot.

						Between Lot Comparison			
						vs 18002-21		vs 18003-21	
Time Point	Lot	N	n	%	(95 % CI)	Difference	(95 % CI)	Difference	(95 % CI)
Pre-Vaccination	18001-21	76	27	35.5	(24.9, 47.3)	4.2	(-10.5, 18.9)	2.5	(-11.3, 16.3)
	18002-21	83	26	31.3	(21.6, 42.4)			-1.7	(-14.9, 11.5)
	18003-21	115	38	33.0	(24.6, 42.4)				
28 Days Post-Vaccination	18001-21	75	68	90.7	(81.7, 96.2)	0.3	(-8.8, 9.5)	-5.8	(-13.2, 1.6)
	18002-21	83	75	90.4	(81.9, 95.7)			-6.1	(-13.3, 1.1)
	18003-21	114	110	96.5	(91.3, 99.0)				

[1] 96-99% of subjects had a level ≥0.1 pre-vaccination, and all subjects had a level ≥0.1 28 days following vaccination.
Values below the LOQ were replaced with 1/2 the LOQ.
N-Number of subjects who provided a measurement. n-Number of subjects attaining the specified titre level.
Source: STN:103171/0.5005, Volume 2, page 297

Table 65. Historical Td-IPV Study: Comparative analysis of the proportion of subjects with a diphtheria antitoxin level ≥0.1[1], by lot.

						Between Lot Comparison			
						vs 18002-21		vs 18003-21	
Time Point	Lot	N	n	%	(95 % CI)	Difference	(95 % CI)	Difference	(95 % CI)
Pre-Vaccination	18001-21	76	44	57.9	(46.0, 69.1)	-9.6	(-24.6, 5.4)	2.2	(-12.1, 16.6)
	18002-21	83	56	67.5	(56.3, 77.4)			11.8	(-1.7, 25.4)
	18003-21	115	64	55.7	(46.1, 64.9)				
28 Days Post-Vaccination	18001-21	75	70	93.3	(85.1, 97.8)	-3.1	(-10.0, 3.9)	-2.3	(-9.1, 4.5)
	18002-21	83	80	96.4	(89.8, 99.2)			0.8	(-4.7, 6.3)
	18003-21	114	109	95.6	(90.1, 98.6)				

Values below the LOQ were replaced with 1/2 the LOQ.
N-Number of subjects who provided a measurement. n-Number of subjects attaining the specified titre.
Source: STN:103171/0.5005, Volume 2, page 296

9.6.5.3 Safety There was substantial variation in the frequency of reported adverse events between the vaccine lots and by study center, which is likely related, in part, to differences in safety monitoring at study sites. At the CB sites, where monitoring was in an informal group setting, few subjects reported any reactions. At the P sites, where subjects were monitored individually, higher frequencies of adverse events were reported. The frequencies of adverse events reported within the first 72 hours following vaccination for subjects enrolled at the P sites is provided in the table below.

Table 66. Historical Td-IPV Study: Proportion of subjects with local and systemic adverse events occurring within the first 72 hours following Td-IPV vaccination, sites with individual subject monitoring for adverse events.

Adverse Event	Severity	SS	N	%	LCL	UCL
Discomfort	Mild	148	95	64.2	55.9	71.9
	Moderate	148	28	18.9	13.0	26.2
	Severe	148	1	0.7	0.0	3.7
Swelling	>5 ≤ 40 mm	148	4	2.7	0.7	6.8
	>40 <100 mm	148	6	4.1	1.5	8.6
Redness	>5 ≤ 40 mm	148	1	0.7	0.0	3.7
Fever	>37 ≤ 38 C	148	42	28.4	21.3	36.4
Malaise	Mild	148	11	7.4	3.8	12.9
	Moderate	148	7	4.7	1.9	9.5
	Severe	148	1	0.7	0.0	3.7
Headache	Mild	148	14	9.5	5.3	15.4
	Moderate	148	12	8.1	4.3	13.7

"SS" indicates samples size; "N" indicates number of subjects
LCL indicates lower confidence limit; UCL indicates upper confidence limit
Source: STN:103171/0.5005, Volume 2, pages 302-303

9.6.6 Reviewer's Comments and Conclusions on the Historical Td-IPV Study

1. As with the study of Td in Canadian Armed Forces Recruits, there were no pre-specified criteria to demonstrate lot consistency, and there was no pre-specified statistical analysis plan or evaluation of statistical power to assess any lot consistency endpoints. In addition, there appeared to be no formal randomization or blinding procedures. Primary equivalence criteria recently recommended by CBER for the evaluation of lot consistency of other vaccines that contain tetanus and diphtheria toxoids that are intended for use as booster vaccination (90% CI for the ratio of lot GMTs not less than 0.67 and not greater than 1.5) were met for all three lot comparisons for tetanus, and for two of three lot comparisons for diphtheria. Recently recommended secondary equivalence criteria (95% CI for the difference in booster response rates not to exceed $\pm$10%), were not met for any of the comparisons.

2. There is limited information on how adverse events were monitored in this study. Methods for monitoring adverse events were not uniform among study sites, and these differences apparently are reflected in the reported frequencies of adverse events. Reported frequencies of local and systemic adverse events were much lower than that reported in more recent studies of Td or Td combination vaccines. Available information suggests that the frequency of adverse events, at least at some study sites, was likely underestimated in this study.

10. OVERVIEW OF EFFICACY (IMMUNOGENICITY) -- ACROSS STUDIES

10.1 Primary immunization

Because of the sample size, the primary immunization study does not fully meet the criteria set forth by the Panel on Review of Bacterial Vaccines and Toxoids. The number of subjects that contributed to the efficacy analysis was lower than the minimum number of subjects needed for an adequate documentation of efficacy according to the Panel (17 vs. 19). However, all 17 subjects evaluated achieved threshold levels of tetanus and diphtheria immunity considered acceptable by the Panel. A previous statistical review at CBER indicated that, with 95% probability, the seroconversion rates for diphtheria and tetanus in this study were at least 80%, the threshold of acceptability set by the Panel.

As discussed previously in Section 4.1 of this review, CBER decided that despite the manufacturing and product differences between the Td used in the primary immunization study and the currently manufactured Td, the data from this study are sufficient to support approval of a primary immunization indication.

10.2 Booster immunization

10.2.1 Limitations of study population with regard to age groups and racial/ethnic groups

No data are available using the candidate Td vaccine in persons $\geq$60 years of age, an age group for which routine Td vaccination is recommended.

For adolescents ages 12-17 years, immunogenicity data from recent studies are limited to 37 subjects who received the candidate Td vaccine. Supportive immunogencity data from recent studies are available on approximately 1,000 adolescents who received the candidate Td vaccine combined with one or more other antigens.

Data on race and ethnicity were not collected in any of the studies, all of which were conducted in Canada. Therefore, the subjects who contributed to the immunogenicity database may not be representative of the U.S. population with regard to race and ethnicity.

10.2.2 Tetanus immunogenicity
The most relevant and most reliable immunogenicity data on booster vaccination with Td are from recent clinical studies in which 426 subjects (389 adults and 37 adolescents) received Td. Supportive immunogenicity data are also available from approximately 1,000 adolescents and approximately 1,000 adults who received Td combined with other antigens in recent studies. The tetanus immunogenicity data on subjects who received Td combined with other antigens were generally consistent with data on subjects who received Td. From studies that included subjects who received Td as well as Td combined with other antigens, there was no evidence that the other antigens substantially affected the immune response to tetanus toxoid.

Among subjects who received Td in recent studies, approximately 90-95%, depending on study and age group, had a protective level of tetanus antitoxin ($\geq$0.1 IU/ml) prior to vaccination. Approximately 10% of adolescents and approximately 55-60% of adults had a pre-vaccination tetanus antitoxin level $\geq$1.0 IU/ml. Post-vaccination, a level $\geq$1.0 IU/ml was achieved by >97% of subjects.

All adolescents and approximately 80% of adults who received Td demonstrated a booster response to tetanus toxoid. Potential reasons for the age-related difference in booster response rates may be that some adults were not adequately primed, some adults who were adequately primed may have had a suboptimal booster response, and some adults with a high pre-vaccination antibody level may not have achieved a four-fold rise after vaccination. The relative contribution of these and other possible factors is not known.

10.2.3 Diphtheria immunogenicity
The most relevant and most reliable immunogenicity data on booster vaccination with Td are from recent clinical studies in which 426 subjects received Td (389 adults and 37 adolescents). Supportive immunogenicity data are also available from approximately 1,000 adolescents and approximately 1,000 adults who received Td combined with other antigens in recent studies. In one study, adults who received TdcP-IPV had a somewhat lower booster response rate to the diphtheria toxoid component than subjects who received Td. Otherwise, the diphtheria immunogenicity data on subjects who received Td combined with other antigens were generally consistent with data on subjects who received Td.

Available data indicate that in most circumstances, a diphtheria antitoxin level of 0.01 IU/ml, as determined by in vivo or in vitro toxin neutralization tests, is the lowest giving some degree of protection, while levels $\geq$0.1 IU/ml may be needed for full protection. Based on data from the historical study of Td in Canadian Armed Forces Recruits, the sponsor assumed that at least 95% of subjects who received Td or Td combined with other antigens in recent studies would achieve a post-vaccination level of diphtheria antitoxin $\geq$0.1 IU/ml. This expectation was met for adolescents. However, in recent studies, among adults who received the candidate Td vaccine, alone or combined with other antigens, the proportion who achieved a diphtheria antitoxin level $\geq$0.1 IU/ml post-vaccination ranged from 83.1%-89.3%, with the lower bound of the 95% confidence interval on the point estimates ranging from 79.0%-82.5%. The proportion of adults in these studies who demonstrated a booster response to diphtheria toxoid ranged from approximately 72%-84%.

As discussed in the comments for individual studies, reasons for the lower than expected diphtheria seroprotection rate among adults are not clear. One potential explanation offered by the sponsor is the older age of adults in recent studies relative to subjects in the historical study among Canadian Armed Forces recruits, and the possibility that some adults in recent studies had not been adequately primed. Alternatively, some adults who were adequately primed may have had a suboptimal response to booster vaccination. Data to reliably assess these possibilities are not available. The clinical relevance of the lower than expected diphtheria seroprotection rates among adults who received the candidate Td, alone or combined with other antigens, is unknown. In the absence of a control arm that received a U.S. licensed Td vaccine, this finding is difficult to interpret.

10.2.4 Clinical data to support manufacturing consistency

As discussed above in Sections 9.5.6 and 9.6.6 of this review, the clinical data from the historical study of Td in Canadian Armed Forces Recruits and from the historical lot consistency study of Td-IPV are not adequate to demonstrate manufacturing consistency of the candidate Td vaccine.

The package insert for the sponsor's DT for Pediatric Use (approved in 1997) includes data from a clinical study conducted in Baltimore, MD, in which 137 infants who received one of three lots of DT at 2, 4, and 6 months of age, had diphtheria and tetanus antitoxin levels evaluated at 8 months of age. After three doses of DT, all subjects had a tetanus antitoxin level $\geq$0.01 IU/ml and 99% had a diphtheria antitoxin level $\geq$0.01 IU/ml. Geometric mean titers for diphtheria and tetanus antitoxin in recipients of the three DT lots were not significantly different, ranging from 0.25 to 0.35 IU/ml for diphtheria antitoxin, and from 0.75 to 0.80 IU/ml for tetanus antitoxin after the third dose. Information on the proportion of subjects with antitoxin levels $\geq$0.1 IU/ml is not provided in the package insert. The data from this study have not been submitted to the Td BLA, but were reviewed by CBER as part of the BLA (STN 103944) for DT. One limitation of this study in supporting manufacturing consistency of Td is the possibility that potential lot-to-lot variability of the diphtheria toxoid component relevant for Td may not have been apparent due to the higher diphtheria toxoid content of DT.

11. OVERVIEW OF SAFETY ACROSS STUDIES

As discussed in the Overview of Immunogenicity, there are also no available safety data on the candidate Td vaccine in persons $\geq$60 years of age, an age group for whom Td vaccine is routinely recommended. The safety database with the candidate Td vaccine in adolescents, another age group targeted by routine recommendations for Td, is limited to 37 subjects. Data on race and ethnicity were not collected in any of the studies, all of which were conducted in Canada. Therefore, the subjects who contributed to the safety database for the candidate Td vaccine may not be representative of the U.S. population with regard to race and ethnicity.

The most relevant and reliable data to support the safety of the candidate Td vaccine are from recent studies in which 37 adolescents and 736 adults less than 60 years of age received a booster dose of Td.

Supportive safety data are available from approximately 2,000 subjects (~1,000 adolescents and ~1,000 adults less than 60 years of age) who received the candidate Td vaccine combined with one or more other antigens in recent studies. In interpreting the data on Td combined with other antigens, one must consider the potential for added reactogenicity due to other antigens, as well as the possibility for underestimation of adverse events associated with Td if other antigens interfere with the immune response to Td. Across studies, overall, there was a tendency for an increased frequency of local adverse events and fever with the addition of antigens in combined vaccines.

In historical studies, 347 subjects received the candidate Td vaccine and 276 received Td combined with other antigens. Nearly all of the subjects enrolled in the historical studies were adolescents or adults less than 30 years of age. Available, limited information from these studies indicates that safety monitoring was less intensive than methods typically used in more contemporary pre-licensure vaccine safety studies.

Local adverse events occurred frequently following vaccination with either Td or Td combined with other antigens. In recent studies, overall, >80% of subjects reported pain at the injection site, approximately 10-20% reported redness, and approximately 10-20% reported swelling. Most solicited local adverse events were mild or moderate in intensity. The frequency of local adverse events was generally highest during the first 24 hours following vaccination.

Fever was reported infrequently among recipients of Td or Td combined with other antigens. When reported, fever was almost always low-grade.

In one study, reported adverse events following Td that were not specifically solicited included swelling of the entire upper limb in one subject (0.3%) and neck symptoms (stiffness, soreness, discomfort, and/or pain) in 11 subjects (3.7%).

Both local and systemic adverse events tended to be reported more frequently among adolescents than adults. This finding may possibly reflect shorter intervals since previous vaccination for adolescents, the generally more robust booster response to Td observed in adolescents, inadequate previous priming in some adults, age-related differences in perception and reporting of adverse events, and/or other factors.

The nature and timing of serious adverse events reported during the course of the recent studies suggest that they were unlikely attributable to vaccination with Td or a Td-containing vaccine.

12. CONCLUSIONS

Available data seem adequate to support the efficacy of the candidate Td vaccine administered as a primary series.

The size of the overall safety database for the candidate Td vaccine is limited, particularly for adolescents. However, there is a substantial supportive safety database on Td combined with other antigens in subjects 11-59 years of age.

There are no safety or immunogenicity data on the candidate Td vaccine in persons 60 years of age or older, an age group for whom Td vaccine is routinely recommended. In one study, a small number of subjects ages 60-65 years of age received TdcP-IPV, even though the age range for eligibility was 12-59 years of age.

There were no major safety concerns evident from the available data on the candidate Td vaccine or Td combined with other antigens. However, interpretation of the safety data on booster immunization with the candidate Td vaccine is hindered by the lack of an appropriate control group.

Given the consistently high proportion of subjects who achieved a level of tetanus antitoxin $\geq$1.0 IU/ml across studies and age groups, the immunogencity data on Td and Td combined with other antigens support the efficacy of the tetanus toxoid component of the candidate Td vaccine, administered as a booster dose. However, an area of concern is the lower than expected seroprotection rate observed for diphtheria among adults who received Td or Td combined with other antigens. In the absence of a control group who received a U.S. licensed Td vaccine, it is difficult to draw conclusions about the clinical relevance of this finding.

There are no animal reproduction studies on the candidate Td vaccine, and no data on the use of this vaccine in pregnant women.
Available data are insufficient to support consistency of manufacturing for the candidate Td vaccine.

13. RECOMMENDATIONS

1. Per current standards, comparative safety and immunogenicity data relative to a U.S. licensed Td would be required for approval of a new Td vaccine. However, given that this license application was initially submitted in 1986 and such data were not requested, the recent shortage of Td in the United States, the entirety of the database with Aventis Pasteur Limited's Td or Td combined with other antigens

that was submitted in support of this application, the wide experience with the sponsor's Td vaccine in Canada, and the sponsor's commitment to conduct a large clinical post-marketing study, as outlined in section 14.1 below, it was decided that the available data would be acceptable for approval of this Td vaccine in persons 7-59 years of age.

2. A post-marketing study should be conducted to obtain additional safety data on booster vaccination with the candidate Td vaccine in approximately 3,000 subjects, with enrollment stratified by age group, to ensure adequate representation of adolescents and adults. The study should be conducted in a population that reflects the racial and ethnic diversity of the U.S. population. All subjects should be followed for a minimum of one month post-vaccination for medically attended adverse events and for six months post-vaccination for serious adverse events. A subset of subjects, e.g., one-third, should be monitored for local and systemic adverse events for 14 days post-vaccination using individual diary cards.

3. In order to obtain a more robust assessment of the immune response to Td booster vaccination in adolescents, in a subset of adolescents (e.g., approximately 300) enrolled in the post-marketing study, pre- and post-vaccination serum samples should be collected for evaluation of diphtheria and tetanus booster responses, rates of seroprotection, and GMTs.

4. Prior to approval of the candidate Td in persons ≥60 years of age, the sponsor should conduct a safety and immunogenicity study in this age group. In view of the lower than expected post-vaccination diphtheria seroprotection rates observed among adults <60 years of age, the evaluation of Td immunogenicity in adults ≥60 years will need to be relative to U.S.-licensed Td vaccine. Inadequate priming and suboptimal immune responses related to aging may result in even lower rates of seroprotection and boosting in adults ≥60 years of age than observed in younger adults. Because it may not be feasible to reliably address the relative contribution of inadequate priming vs. suboptimal responses, comparison to a control group will be critical to enable interpretation of the results.

A study to support approval of Td in persons ≥60 years of age, should be designed to evaluate non-inferiority of the candidate Td relative to U.S. licensed Td, with seroprotection rates at the ≥0.1 IU/ml level and booster response rates assessed as co-primary endpoints for diphtheria and tetanus. Secondary comparative analyses of GMTs and seroprotection rates at the ≥1.0 IU/ml level should also be conducted for both antigens.

The study should be of sufficient size to detect adverse events that occur at a rate of approximately 1%. Subjects should be monitored for local and systemic adverse events for 14 days post-vaccination using individual diary cards. Subjects should also be followed for a minimum of one month post-vaccination for medically attended adverse events and for six months post-vaccination for serious adverse events.

The study population should reflect the racial and ethnic diversity of the U.S. population.

5. Because the candidate Td vaccine is targeted to an age range of childbearing potential, a reproductive toxicology with this vaccine should be conducted.

6. Data to support manufacturing consistency of the candidate Td vaccine are needed. ----------
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14. POST-MARKETING EVALUATION OF Td

Prior to licensure, APL made commitments to conduct additional post-marketing studies or to complete ongoing studies, as outlined below.

14.1 Study TDC01-- Immunogenicity and Safety of Canadian Manufactured Tetanus and Diphtheria Toxoids Adsorbed (Td) for Adult Use Vaccine compared with U.S. Manufactured Tetanus and Diphtheria Toxoids Adsorbed for Adult Use Vaccine in Persons 60 Years of Age and Older, and Immunogenicity and Safety of Canadian Td Vaccine in Persons 11 Through 59 Years of Age

BACKGROUND
In the study outlined below, the sponsor plans to enroll subjects 11-59 years of age, an age group for which the Canadian Td is expected to be approved, as well as subjects ≥60 years of age, an age group for which the sponsor intends to seek a new indication. There are currently no available data on the Canadian Td in persons ≥60 years of age, and the sponsor anticipates that the data from this study will be sufficient for approval of this vaccine in this age group. Because the study will include an age group for whom the vaccine will not be approved, the sponsor has agreed to submit an IND for their Canadian Td, and to conduct this study under the IND.

The sponsor has agreed to submit the final study protocol for TDC01 by the end of December 2003, and to initiate the study by April 2004 or 2 weeks after CBER releases the first commercial batch of the candidate Td, whichever is later. The sponsor has committed to submit their first commercial final bulk batch of Td to CBER by April 2004. The sponsor anticipates that patient accrual for this study will be completed 20 months after the first subject is enrolled, and that the study will be completed 6 months after the last subject is enrolled. The sponsor has committed to submit the final study report 1 year after completion of follow-up of the last subject.

CLINICAL TRIAL OUTLINE [based on synopsis submitted 9/19/03: STN 103171/0.5016)]

Protocol #: TDC01, version 3

Phase: The portion of the study in persons 60 years of age and older is considered a phase III study to support a new age indication. The portion of the study in subjects 11-59 years of age is considered phase IV.

Objectives:

Primary
1. To compare the post-vaccination levels of antibody to Canadian Td to levels of antibody to U.S. Td, when administered to persons 60 years of age and older.

Observational

1. To describe the levels of antibody pre- and one-month post vaccination for tetanus and diphtheria toxoids for subsets of adolescents (11-14 and 15-18 years of age), for a subset of adult 19-59 years of age, and for a subset of persons 60 years and older.

2. To describe the safety profile of all subjects for the following:
- immediate reactogenicity
- solicited local and systemic adverse events for Days 0 to 3, 0 to 7, and 8 to 14 days post-vaccination
- medically attended adverse events from vaccination until visit 3 (28-42 days post-vaccination)

- serious adverse events from vaccination to six months post-vaccination

3. To describe the relationship between local reactions and time since the last previous tetanus and diphtheria immunization.

Design: Randomized, partially double-blind, multi-center trial conducted in the U.S. Participants will be assigned to one of three treatment groups, as follows, with subjects ages 60 years and older randomized to one of two groups:

- One open-labeled group ages 11-59 years will receive Canadian Td on Day 0
- One group, double-blinded, ages 60 years and older will receive U.S. Td on Day 0
- One group, double-blinded, ages 60 years and older will receive Canadian Td on Day 0

The sizes of the groups, by age, is shown in the table below:

Table. Number of subjects who will be evaluated for safety and immunogenicity, by age group and vaccine

Age (years)	Safety		Immunogenicity	
	Canadian Td	U.S. Td	Canadian Td	U.S. Td
11-14	750	0	250	0
15-18	750	0	250	0
19-59	750	0	250	0
≥60	750	400	400	400
Total	3000	400	1150	400

Study Population: The study will be conducted in the U.S. at sites that are to be determined.

Inclusion criteria:

- Healthy as determined by medical history
- At least 11 years of age at the time of vaccination
- Provides informed consent/assent form
- Provides history or documentation of primary immunization against diphtheria and tetanus

Exclusion criteria:

- Serious chronic disease (i.e., cardiac, pulmonary, renal, neurologic, metabolic, rheumatologic, etc.)
- Known or suspected impairment of immunologic function
- Acute medical illness with or without fever within the last 72 hours or an oral temperature ≥100.4°F (≥38°C) at the time of enrollment
- Administration of immune globulin or other blood products within the last three months, or corticosteroids (injected or oral) or other immunomodulator therapy within six weeks of the study vaccine. Individuals on a tapering dose of oral steroids may be included, as long as steroids were discontinued within two weeks prior to enrollment.
- Antibiotic therapy within 72 hours prior to vaccination
- Received any vaccine in the 28-day period prior to enrollment, or scheduled to receive any vaccination other than influenza prior to the one month visit
- Known or suspected hypersensitivity to Td components, thimerosal or latex rubber
- Unable to attend scheduled visits or to comply with study procedures

- Enrolled in another clinical trial
- Any condition, which in the opinion of the investigator, would pose a health risk to the participant or interfere with evaluation of the vaccine
- In females of childbearing potential, a positive urine pregnancy test at the time of vaccination
- Females who have not abstained from sexual intercourse or used adequate contraceptive precautions during the one month prior to enrollment
- Lactating females
- Subjects who report a history of Guillain Barre syndrome within 6 weeks after a previous dose of tetanus toxoid-containing vaccine
- Subjects who report a previous history of diphtheria or tetanus

Vaccination schedule: Subjects 11-59 years of age will receive one dose of Canadian manufactured Td at Visit 1. Subjects ≥60 years of age will receive one dose of either Canadian manufactured Td or U.S. manufactured Td at Visit 1.

Primary Endpoints ***(for subjects 60 years of age and older)***

Antigen	Endpoints	Non-inferiority criteria
Diphtheria toxin	% ≥0.1 IU/ml (one month post vaccination) booster response (pre- to post vaccination)	UL of 95% CI for δ (U.S.Td – Canadian Td) <10%
Tetanus toxin	% ≥0.1 IU/ml (one month post vaccination) booster response (pre- to post vaccination)	UL of 95% CI for δ (U.S.Td – Canadian Td) <10%

Booster response analyses will be based on pre-vaccination titers, as follows:

Tetanus booster response:
- if pre-vaccination titer <0.1 IU/ml: 4-fold rise and a post-vaccination titer ≥0.1 IU/ml
- if pre-vaccination titer >0.10 IU/ml and ≤5.3 IU/ml: 4-fold rise
- if pre-vaccination titer >5.3 IU/ml: excluded from analysis

Diphtheria booster response:
- if pre-vaccination titer <0.1 IU/ml: 4-fold rise and a post-vaccination titer ≥0.1 IU/ml
- if pre-vaccination titer >0.10 IU/ml and ≤1.28 IU/ml: 4-fold rise
- if pre-vaccination titer >1.28 IU/ml: excluded from analysis

Observational Endpoints

Immunogenicity
For diphtheria and tetanus antibodies, overall, and for each age group (11-14 years, 15-18 years, 19-59 years, and ≥60 years):

- Distribution of frequencies
- Reverse cumulative distribution curves

- One-month post-vaccination seroprotection rates at levels ≥0.01, ≥0.1, and ≥1.0 IU/ml, and 95% confidence intervals
- Pre- and post-vaccination antibody GMTs and 95% confidence intervals
- Booster response rates 95% confidence intervals
- Four-fold response rates and the 95% confidence intervals

Safety
For the overall groups and for each age group (11-14 years, 15-18 years, 19-59 years, and ≥60 years):

- Solicited adverse events, by severity for Days 0-3, 0-7, and 8-14, with 95% confidence intervals
- Unsolicited adverse events that result in a medical encounter from day 0 through one month post-vaccination
- Immediate reactions that occur within 15 minutes after vaccination
- Serious adverse events that occur within 6 months post-vaccination
- Deaths that occur within 6 months post-vaccination
- Withdrawals due to adverse events
- Rates of solicited and unsolicited adverse events by time since last previous Td vaccination (0-<3 years, 3-<5 years, 5-<10 years, and ≥10 years).

Statistical Considerations
Although not provided in the synopsis, the table below summarizes available data from the BLA on diphtheria and tetanus seroprotection rates and booster response rates following the sponsor's Canadian Td in adults 18-59 years of age.

Table. Proportion of adults 18-59 years of age with post-vaccination diphtheria and tetanus antibody levels ≥0.1 IU/ml and with booster responses to diphtheria and tetanus toxoids following booster immunization with Td.

		N	**% ≥0.1 IU/ml (95% CI)**	**% with booster response[1] (95% CI)**
Diphtheria	Study A	263	84.8 (79.9, 88.9)	77.6 (72.0, 82.5)
	Study B	122	89.3 (82.5, 94.2)	83.6 (75.8, 89.7)
Tetanus	Study A	263	99.6 (97.9, 100)	80.6 (75.3, 85.2)
	Study B	122	100 (97.0, 100)	81.2 (73.1, 87.7)

[1] Booster response is defined as a ≥4-fold increase in post-vaccination anti-toxin level, relative to pre-vaccination level; subjects whose pre-vaccination level was <0.1 IU/ml must also have a post-vaccination level ≥0.1 IU/ml to be considered a responder.

In the synopsis provided, the sample size calculations for the assessment of immunogenicity in adults ≥60 years of age were based on the planned non-inferiority analyses of diphtheria and tetanus seroprotection rates for the Canadian Td relative to the U.S. Td. The co-primary endpoints of booster response rates for tetanus and diphtheria were not addressed. Since there are no available immunogenicity data on the Canadian Td in adults ≥60 years of age, the expected diphtheria and tetanus seroprotection rates were estimated based on available data in younger adults (see previous table for available data). For the sample

size calculations, the expected seroprotection rate for diphtheria (i.e., proportion with antibody level ≥0.1 IU/ml) was estimated to be 80%, and the expected seroprotection rate for tetanus (i.e., proportion with antibody level ≥0.1 IU/ml) was estimated to be 90%. Assuming an attrition rate as high as 12%, with an immunogenicity subset of 400 subjects ≥60 years of age in each vaccine group, there would be 351 subjects evaluable for immunogenicity in each group. With this number of evaluable subjects, the study has 90% power to evaluate non-inferiority of diphtheria seroprotection rates, 99% power to evaluate non-inferiority of tetanus seroprotection rates, and 90% power overall.

Study Visits and Phone Calls Contacts with subjects are scheduled as follows:

Visit 1 (day 0)
- enrollment and vaccination (all subjects)
- obtain serum from immunogenicity subset

Visit 2 (day 15-22 post-vaccination)
- diary card collected from all subjects

Visit 3 (day 28-42 post-vaccination)
- inquiry about medically attended adverse events for all subjects
- obtain serum from immunogenicity subset

Six-month phone call
- inquiry about serious adverse events for all subjects

Study Procedures to Assess Immunogenicity
Serum samples will be collected from a subset of subjects prior to vaccination, and 28-42 days following vaccination. Serum samples will be tested for levels of antibody to tetanus and diphtheria toxins. The assays were not specified.

Study Procedures to Assess Safety

Initial observation After vaccination, each subject will be observed for 15 minutes.

Solicited adverse events: Subjects will keep a diary card to record information on solicited local and systemic adverse events on days 0-14 after vaccination. Subjects will be provided with a ruler for measuring the sizes of local reactions, and with a digital thermometer for measuring body temperature. The diary cards will be collected at the second study visit (day 15-22 following vaccination).

Medically attended adverse events: Information will be collected on medically attended adverse events that occur from Day 0 to Visit 3 (Day 28-42).

Serious adverse events: A six-month follow-up telephone call will be made to inquire about serious adverse events.

COMMENTS/QUESTIONS TO CONVEY TO SPONSOR

General Comment
1. The overall plan for the evaluation of safety and immunogenicity of your candidate Td vaccine in subjects 11-59 years of age is acceptable. However, for reasons outlined in the specific comments below, we do not consider your proposal adequate to support approval of your candidate Td vaccine in subjects

≥60 years of age. Please note that while some of the comments below pertain only to subjects ≥60 years of age (e.g., non-inferiority immunogenicity analyses), others pertain to younger age groups as well (e.g., definition of booster response).

Specific Comments

2. You plan to enroll subjects in the study irrespective of the interval since their last dose of Td. However, as stated in the package insert for your Canadian Td, a booster dose of Td is recommended at 11-12 years of age if at least 5 years have elapsed since the last dose of tetanus and diphtheria toxoid containing vaccine. Subsequent routine boosters are recommended every 10 years. More frequent administration of Td is not recommended except under circumstances of wound management or diphtheria prophylaxis since it may be associated with increased incidence and severity of adverse reactions.

a. As we previously discussed in the telecon of July 23, 2003, for subjects 13-59 years of age, a minimum interval of 5 years since previous vaccination with a diphtheria or tetanus toxoid containing vaccine would be acceptable if the informed consent form adequately addresses the potential risk for increased rates and severity of adverse events. However, we do not feel that an interval since last vaccination of <5 years is justified.

b. If you decide to allow a minimum interval of 5 years since previous vaccination for subjects 13-59 years of age, we recommend that you stratify the immunogenicity analyses by time since previous vaccination, as you intend to do for the safety analyses.

c. For subjects 60 years of age and older, an age group for which there are no safety and immunogenicity data for your Canadian Td, we recommend that the minimum interval since previous vaccination with a diphtheria or tetanus toxoid-containing vaccine be at least 10 years, to avoid confounding the interpretation of the safety and immunogenicity data.

3. In the absence of immunogenicity data on booster immunization with Td in persons ≥60 years of age from a phase 2 study, it is difficult to arrive at the assumptions for immune responses that are needed to determine the appropriate sample size for your pivotal study in this age group. Your statistical analysis plan for the primary non-inferiority analyses of tetanus and diphtheria seroprotection rates in persons ≥60 years of age only allows for expected post-vaccination seroprotection rates of 90% and 80%, respectively. If the observed seroprotection rates are lower than the rates you have estimated, the study may not be adequately powered to assess non-inferiority of the seroprotection rates following your Canadian Td relative to the currently licensed Td, and thus, may not be sufficient to support approval in this age group. Please respond.

4. Based on data from Studies TD9704 and TD9707, nearly 100% of adults 18-59 years of age who received a booster dose of your Canadian Td had a post-vaccination tetanus antitoxin level ≥0.1 IU/ml. In view of the potentially high post-vaccination seroprotection rate for tetanus, we recommend that for the primary non-inferiority analysis of tetanus seroprotection rates in subjects ≥60 years of age, you use a 5% non-inferiority margin, rather than a 10% margin to determine the sample size of the immunogenicity subset. If the observed post-vaccination seroprotection rate for tetanus is very high in subjects ≥60 years of age who receive the control Td vaccine (e.g., similar to that observed for your candidate Td in younger adults), we would consider your candidate Td vaccine non-inferior with regard to tetanus seroprotection if the proportion of subjects protected is not more than 5% lower than that observed for the control vaccine (based on the lower bound of the 95% confidence interval for the difference). If the observed seroprotection rate in the control group is lower than that previously observed in younger adults who received your Canadian Td, as you have assumed, we would likely accept a 10% non-inferiority margin.

5. You have not provided sample size and statistical power calculations for the non-inferiority analyses of booster response rates for tetanus and diphtheria in subjects ≥60 years of age who receive your Canadian manufactured Td vs. the currently licensed Td. Since we view these as important co-primary analyses for evaluation of your Canadian Td in subjects ≥60 years of age, these endpoints should be taken into consideration in determining the appropriate size of the immunogenicity subset in this age group. Moreover, if the expected booster response rates for tetanus and diphtheria are lower than the expected seroprotection rates, as suggested by the available data on your candidate Td vaccine in adults 18-59 years of age, the sample size required for the non-inferiority analyses of booster response rates may be higher than that for the analyses of seroprotection rates. Therefore, please provide sample size and statistical power calculations for these analyses.

6. Subjects with a pre-vaccination tetanus antitoxin titer >5.3 IU/ml will be excluded from the analyses of tetanus booster response rates, and subjects with a pre-vaccination diphtheria antitoxin titer >1.28 IU/ml will be excluded from the analyses of diphtheria booster response rates. In contrast, in Study Td506, being conducted under IND 9226, in which your investigational vaccine, Diphtheria and Tetanus Toxoids and Acellular Pertussis Component Vaccine, Adsorbed (TdcP) has been compared to U.S. licensed Td in adolescents and adults, for subjects whose pre-vaccination antibody level is >5.3 IU/ml for tetanus and >1.28 IU/ml for diphtheria, a booster response is defined as a 2-fold increase in antibody level.

a. Please explain how the threshold pre-vaccination levels of tetanus antitoxin (≤5.3 IU/ml) and diphtheria antitoxin (≤1.28 IU/ml) being used for inclusion in the analysis of booster response rates were arrived at.

b. Please provide a justification for exclusion of subjects with a pre-vaccination tetanus antitoxin level >5.3 IU/ml and a pre-vaccination diphtheria antitoxin level >1.28 IU/ml from the analysis of booster response rates in Study TDC01, in view of the fact that a 2-fold rise in antibody level was used to define a booster response for such subjects in Study Td506.

7. The following comments pertain to the additional immunogenicity analyses that you have listed on page 9 of the synopsis (i.e., in addition to the primary immunogenicity analyses).

a. For subjects 60 years of age and older, we recommend that you provide comparative analyses of the post-vaccination GMTs for tetanus and diphtheria for your Canadian-manufactured Td relative to the U.S. licensed Td. For these analyses, please provide the ratio of GMTs (U.S. licensed Td vs. Canadian Td) and the 90% confidence intervals for the ratio. Since we consider these important secondary analyses for this age group, please also provide statistical power calculations, using a non-inferiority criterion that the upper limit of the 2-sided 90% confidence interval for the ratio of GMTs (U.S. licensed Td/Canadian Td) is less than 1.5.

b. For subjects 60 years of age and older, we recommend that you perform comparative analyses of the proportion of subjects with post-vaccination antibody levels ≥1.0 IU/ml for both diphtheria and tetanus, using the same methods as for the primary endpoint non-inferiority analyses.

c. In addition to providing post-vaccination seroprotection rates (≥0.01, ≥0.1, and ≥1.0 IU/ml) and the 95% confidence intervals, we also recommend that you provide pre-vaccination seroprotection rates for all three specified levels, with 95% confidence intervals, for both tetanus and diphtheria, stratified by age group.

8. Please provide all safety and immunogenicity analyses stratified by gender, in addition to analyses with male and female subjects combined.

9. On page 2 of the protocol, you indicate that you intend to monitor for medically attended events that occur from vaccination through visit 3 (28-42 days post-vaccination). On page 8 of the synopsis, you indicate that you will tabulate and summarize unsolicited adverse events that result in a medical encounter.

a. We recommend that you also collect information on solicited adverse events that result in a medical encounter.

b. For subjects 60 years of age and older, we recommend that you also collect information on unsolicited adverse events for which medical attention is not sought through at least 14 days post-vaccination.

10. Please submit a full study protocol. The protocol should clearly indicate any differences in study procedures for subjects 11-59 years of age and for subjects ≥60 years of age.

11. Please submit copies of all study forms that will be used in the study. If different study forms are to be used for subjects 11-59 years of age and subjects ≥60 years of age, please submit both versions.

12. As previously conveyed in the August 8, 2003 telecon, because your study will include an age range outside of that approved, you will need to submit an IND for your Td vaccine, and conduct the study under IND.

14.2 Study 407/191—Td Adsorbed – Developmental toxicity study in the rabbit by the intramuscular route.

Because the candidate Td vaccine is targeted to an age range of childbearing potential, CBER recommended that a reproductive toxicology study be conducted with this vaccine. CBER has reviewed the protocol for this study (submitted as part of STN 103171/0.5011), and provided comments to the sponsor. The study is ongoing and the sponsor has agreed to submit the final report to BLA 103171 by the end of May 2004.

To support manufacturing consistency of the candidate Td vaccine, ----------