FDA Statistical Review and Evaluation

Document for the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

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ADACEL™: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)

Indication: Single-dose immunization for the prevention of tetanus, diphtheria, and pertussis in persons aged 11 through 64 years of age

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This statistical briefing document covers two pivotal clinical trials for this application. Study Td506 is a large-scale safety and immunogenicity study to assess non-inferiority of Tdap vaccine in healthy adults and adolescents as compared to a currently licensed Td vaccine. Study Td505 is to assess the consistency of Tdap vaccine in healthy adolescents using three consecutively manufactured lots.

I. STUDY Td506

Title: "Safety and Immunogenicity of Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (TdcP) Vaccine Compared to Tetanus and Diphtheria Toxoids Adsorbed (Td) in Adolescents and Adults 11-64 Years of Age"

Study Design

This was a Phase 3, randomized, controlled, modified double-blind*, multicenter study designed (1) to assess the safety and immunogenicity of Tdap vaccine when given as a booster dose in subjects who had been previously primed with the respective antigens, and (2) to compare the safety and immunogenicity of Tdap vaccine to a licensed Td vaccine and to historical controls. Participants ranged in age from 11 to 64 years and at enrollment were stratified into 5 age ranges (11 to 13; 14 to 17; 18 to 28; 29 to 48; and 49 to 64 years of age).

(*) The participant, the investigator and sponsor personnel were blinded to which vaccine was administered.

Primary Objectives

1. To assess the immunogenicity of the Diphtheria and Tetanus Toxoids of Tdap vaccine compared to a licensed Td vaccine. 2. To assess the immunogenicity of the pertussis antigens of the Tdap vaccine compared to the immune responses from the Sweden I Efficacy trial (DAPTACEL®) and supportive trials conducted in Canada with Tdap vaccine.

Primary Hypotheses

The following hypotheses were to be addressed for adolescents 11 to 17 years of age and adults 18 to 64 years of age, separately.

1a. The anti-diphtheria toxin and anti-tetanus toxin responses for participants who receive Tdap vaccine will be non-inferior to responses observed in participants who receive Td vaccine after a single vaccination, assessed as the comparison of seroprotection rates at the ≥0.1 IU/mL level using the difference in rates between the groups.

1b. The anti-diphtheria toxin and anti-tetanus toxin booster responses for participants who receive Tdap vaccine will be non-inferior to the booster responses elicited by the licensed Td vaccine; a booster response is defined as a four-fold response for participants with a pre-vaccination titer equal to or below the pre-defined cut-off level and a two-fold response for participants with pre-vaccination titers above the cut-off levels. The cut-off levels are 2.56 IU/mL for diphtheria and 2.7 IU/mL for tetanus.

2a. The anti-pertussis [PT, FHA, FIM, and PRN] responses for participants who receive Tdap vaccine will be non-inferior to responses observed in recipients 1 month after completing a primary series of DAPTACEL® (Sweden I Efficacy trial) at 2, 4, and 6 months of age, assessed as the comparison of GMCs using the ratio of GMCs of Tdap vaccine and DAPTACEL®.

2b. The anti-pertussis [PT, FHA, FIM, and PRN] boosting responses for participants who receive Tdap vaccine will be comparable to acceptable booster responses defined from the data observed in the Aventis Pasteur supportive trials with Tdap vaccine (81.2% for PT, 77.6% for FHA, 82.4% for FIM, 86.4% for PRN); a booster response is defined as a four-fold response for participants with a pre-vaccination titer equal to or below the pre-defined cut-off levels and a two-fold response for participants with pre-vaccination titers above the cut-off level. The cut-off levels are: for PT 85 EU/mL, for FHA 170 EU/mL, for FIM 285 EU/mL, for PRN 115 EU/mL, respectively.

Determination of Sample Size

Planned enrollment was 4400 participants, with 3000 participants in the Tdap vaccine group and 1400 in the Td vaccine group. A total of 2700 participants were to be bled for the immunogenicity assessment.

The sample size and power calculations were done for both primary and secondary endpoints using the non-inferiority approach. The non-inferiority margin (the relative effect deemed important to rule out) was set to 10% for the comparison of rates and 1.5 fold for the comparison of GMCs.

Predicted responses used in the sample size calculation were estimated from the observed data in previous trials with Tdap vaccine and are listed in the following two tables.

Table 1: Predicted Booster Response Rates Levels for Diphtheria and Tetanus

Antigen	Pre-Vaccination Titer Cut-off Value	Predicted Booster Response Level*	Power ($\alpha = 0.025$)
Diphtheria IU/mL	2.56 IU/ mL	92.9%	>99%
Tetanus IU/mL	2.70 IU/ mL	81.6%	98.9%

(*) Predicted booster response rates used for sample size calculation were estimated from the observed data from both adolescents and adults in TC9704(1) and TD9805(5).

As the testing of the primary hypotheses is done for adolescents and adults separately, the power calculations for booster rates were done using the sample size of 540 adolescents in the adolescent and adult groups. There are 810 adults in the Tdap vaccine group and 540 adults in Td vaccine group, so the power estimate for adults will exceed the power estimate for adolescents.

Table 2: Predicted and Acceptable Boosting Response Rates for PT, FHA, FIM, and PRN

Antigen	Pre-Vaccination Titer Cut-off Value	Predicted[1] Response Rates	Acceptable[2] Response Rates	Power[3] α=0.025
PT (EU/mL)	85 EU/mL	91.2%	81.2%	> 99%
FHA (EU/mL)	170 EU/mL	87.6%	77.6%	> 99%
FIM (EU/mL)	285 EU/mL	92.4%	82.4%	> 99%
PRN (EU/mL)	115 EU/mL	96.4%	86.4%	> 99%

[1] Predicted response rates used in the sample size calculation were estimated using the supportive trials TC9704 and TD9805 from the observed data in 581 participants for all antigens but PT. For PT, 570 participants were used.
[2] Acceptable response rates are rates 10% lower than predicted ones.
[3] As the testing of the primary hypotheses is done for adolescents and adults separately, the power calculations were done using the sample size of 540 adolescents. There are 810 adults in the TdcP vaccine group and 540 adults in the Td vaccine group, so the power estimate for adults will exceed the power estimate for adolescents.

Statistical Methods

In general, the continuous variables were presented by summary statistics (i.e., mean, standard deviation, geometric mean concentrations (GMCs) and their confidence intervals) and the categorical variables by frequency distributions (i.e., frequency counts, percentages, and their confidence intervals). It was assumed that log antibody titer for each antigen follows the normal distribution. To establish non-inferiority according to the primary and secondary hypotheses, statistical testing between the groups was performed

using two-sided 95% confidence intervals on the difference in rates and two-sided 95% confidence intervals on ratios of GMCs.

To address the primary hypotheses and the secondary hypothesis, statistical testing between groups was performed within adolescents and adults, using the 2-sided 95% confidence interval on the difference in rates or ratios of GMCs. To calculate the confidence interval for the difference between two proportions, the Mantel-Haenszel method was used, as described in 'Statistical Methods for Rates and Proportions' by Joseph L. Fleiss, page174. This method is based on the weighted average of differences between proportions in the two groups over the strata. For these data, the strata were defined based on subjects' age (adolescents and adults).

The weighted average is calculated as

$$\bar{d} = \sum_{i=1}^{g} \frac{n_{i1} n_{i2}}{n_{i.}} (p_{i1} - p_{i2}) \Big/ \sum_{i=1}^{g} \frac{n_{i1} n_{i2}}{n_{i.}} \quad ,$$

where n_{i1}, p_{i1} are the sample size and proportion of the first group and n_{i2}, p_{i2} are the sample size and proportion of the second group in strata i.

The standard error for the CIs is derived as follows:

$$se(\bar{d}) = \sqrt{\sum_{i=1}^{g} \left(\left(\frac{n_{i1} n_{i2}}{n_{i.}} \right)^2 \left(\frac{p_{i1} q_{i1}}{n_{i1}} + \frac{p_{i2} q_{i2}}{n_{i2}} \right) \right)} \Big/ \sum_{i=1}^{g} \frac{n_{i1} n_{i2}}{n_{i.}}$$

$$q_{i1} = 1 - p_{i1} \ , \ q_{i2} = 1 - p_{i2} \text{ and } n_{i.} = n_{i1} + n_{i2}$$

<u>Safety</u>

For 'Any' and 'Moderate and Severe' Erythema, Swelling, Pain, and Fever rates during Days 0-14, the non-inferiority of Tdap vaccine to Td vaccine will be concluded if the upper limit of the two-sided 95% CI for the difference in event rates is <10%.

<u>Immunogenicity</u>

Per the primary hypotheses 1a and 1b, for diphtheria and tetanus, the non-inferiority of Tdap vaccine to Td vaccine will be concluded if the lower limits of the 2-sided 95% CIs of the difference in post-vaccination seroprotection rates (at the level of ≥ 0.1 IU/mL) and booster rates between the two groups are above –10% (i.e., negative 10%).

Per primary hypothesis 2a, for each pertussis antigen, the non-inferiority of Tdap vaccine to DAPTACEL® (Sweden I Efficacy trial) will be concluded if the lower limit of the 2-sided 95% CI of the post-vaccination GMCs ratio between the two vaccines is above 0.67.

Per primary hypothesis 2b, for each pertussis antigen, the booster response for Tdap vaccine will be comparable to the booster response observed in the supportive trials if the

lower limit of the two-sided 95% CI for the booster rate in Tdap vaccine is above the acceptable booster rate defined from the data observed in the supportive trials. The acceptable booster response rates are: 81.2% for PT, 77.6% for FHA, 82.4% for FIM, and 86.4% for PRN.

Results and Conclusions

A total of 4501 participants were enrolled, of which 4480 were randomized and 4461 were vaccinated, as shown in Table 3. For 30 of these vaccinated participants, it could not be determined with certainty which vaccine they received; of the remaining 4431 participants, 3017 received Tdap vaccine and 1414 received Td vaccine. A subset of study participants (2720 participants) were bled for immunogenicity assessment, of which 18 had unknown vaccine administration, one participant did not receive the vaccine, and 92 participants from Site 119 were not included in the Intent-to-Treat immunogenicity analysis. A total of 84.4% (2296/2720) of the bled participants were in compliance with the protocol for immunogenicity assessment: 84.4% (1270/1504) of Tdap vaccine recipients, 85.6% (1026/1198) of Td vaccine recipients. Both study groups were comparable in participant disposition and demographic characteristics.

Table 3: Participant Disposition

		Tdap		Td		All	
Age	Study Termination Information	n	%	n	%	n	%
11-17	Enrolled and Randomized	1225	100.0	818	100.0	20531	100.0
	Completed Visit 2	1208	98.6	812	99.3	20291	98.8
	Completed entire study	1194	97.5	802	98.0	20051	97.7
	Terminated the Study (early)	31	2.5	16	2.0	48	2.3
18-64	Enrolled and Randomized	1807	100.0	600	100.0	24272	100.0
	Completed Visit 2	1780	98.5	594	99.0	23942	98.6
	Completed entire study	1720	95.2	575	95.8	23152	95.4
	Terminated the Study (early)	87	4.8	25	4.2	112	4.6
Total 11-64	Enrolled and Randomized	3032	100.0	1418	100.0	44803	100.0
	Completed Visit 2	2988	98.5	1406	99.2	44233	98.7
	Completed entire study	2914	96.1	1377	97.1	43203	96.4
	Terminated the Study (early)	118	3.9	41	2.9	160	3.6

Comparison of Seroprotection Rates

As per the primary hypothesis 1a that Tdap vaccine is non-inferior to Td vaccine with respect to seroprotection rates, both **diphtheria and tetanus** meet the –10% criterion for the lower limits of the 95% CIs for the differences in 1-month post-vaccination seroprotection rates between the Tdap vaccine group and Td vaccine group for both age groups, as shown in Table 4. The lower limit of the 95% confidence interval for the difference between Tdap and Td vaccines was -0.53% and -3.55% in adolescents and adults, respectively, and for the entire 11 to 64 year-old population was -1.92% for **diphtheria**. The lower limit of the 95% confidence interval for the difference between

Tdap and Td vaccines was 0.00% and -0.19% in adolescents and adults, respectively, and for the entire 11 to 64 year-old population was -0.10% for **tetanus**.

Table 4: Seroprotection Rates Between Tdap and Td Groups (PPI Population*)

Antigen	Age in Years	1 Month Post-vaccination				
		Tdap Rate %	Td Rate %	Diff %	LCL	UCL
Diphtheria	11-17	99.8	99.8	0.00	-0.53	0.54
	18-64	94.1	95.1	-1.01	-3.55	1.53
	11-64	96.7	97.3	-0.54	-1.92	0.85
Tetanus	11-17	100.0	100.0	0.00	0.00	0.00
	18-64	100.0	99.8	0.20	-0.19	0.58
	11-64	100.0	99.9	0.11	-0.10	0.31

* Per-Protocol Immunogenicity Population is defined as all participants who were randomized, received assigned vaccine, and were bled to have the data according to the protocol.

Comparison of Booster Response Rates

As per the primary hypothesis 1b that Tdap vaccine is non-inferior to the Td vaccine with respect to the 4-fold rise booster rates, both diphtheria and tetanus meet the –10% criterion. That is, the lower limits of the 95% CIs for the differences in 1-month post-vaccination booster rates between Tdap and Td vaccine groups are above -10% for both adolescents and adults, and for the entire study population, as shown in Table 5 below.

Table 5: Booster Response Rates Between Tdap and Td Groups (PPI Population*)

Antigen	Years	Tdap Rate %	Td Rate %	Difference %	LCL	UCL
Diphtheria	11-17	95.1	95.0	0.11	-2.53	2.76
	18-64	87.4	83.4	4.02	-0.01	8.04
	11-64	91.0	88.8	2.20	-0.28	4.69
Tetanus	11-17	91.7	91.3	0.37	-3.02	3.76
	18-64	63.1	66.8	-3.72	-9.09	1.64
	11-64	76.3	78.1	-1.83	-5.11	1.45

* Per-Protocol Immunogenicity Population is defined as all participants who were randomized, received assigned vaccine, and were bled to have the data according to the protocol.

Comparison of Geometric Mean Concentrations

Statistical comparisons of diphtheria and tetanus GMCs using the 95% confidence interval for the GMC ratio between Tdap vaccine and Td vaccine showed non-inferiority of Tdap vaccine to Td vaccine. Table 6 below shows that the lower limits (LCL) of the 95% CIs of GMC ratios 1-month post-vaccination are above 0.67, both for adolescents and adults, as well as for the entire study population.

Table 6: Geometric Mean Concentrations Between Tdap and Td (PPI Population*)

Antigen	Years	Tdap GMC	Td GMC2	GMC Ratio	LCL	UCL
Diphtheria	11-17	8.462	7.096	1.19	**1.03**	1.39
	18-64	2.487	2.368	1.05	**0.86**	1.29
	11-64	4.137	4.119	1.12	**0.98**	1.27
Tetanus	11-17	12.869	14.346	0.90	**0.84**	0.96
	18-64	7.651	8.179	0.94	**0.86**	1.01
	11-64	9.495	10.853	0.92	**0.87**	0.97

* Per-Protocol Immunogenicity Population is defined as all participants who were randomized, received assigned vaccine, and were bled to have the data according to the protocol.

Comparison of TdcP Vaccine to Sweden I Pertussis Results

As per the primary hypothesis 2a that the pertussis immune responses to Tdap vaccine are non-inferior to those responses observed in the subset of DAPTACEL® recipients from the Sweden I Efficacy trial who were tested in the ADACEL™ Serology Bridging study, the results are shown in the following Tables 7 and 8 for adolescents and adults, respectively. GMCs for the Tdap vaccine are consistently higher than the Sweden I Efficacy trial levels for all pertussis antigens, both for adults and adolescents. That is, the lower limits of the 95% CIs for the ratio of GMCs for all pertussis antigens are above 0.67.

Table 7: Comparisons of Pertussis Antigens Between Tdap in Td506 (Adolescents, 11-17 Years, PPI Population*) and DAPTACEL in the Sweden I Efficacy Trial

Antigens	Time	Tdap Td506 Trial		DAPTACEL Sweden I Efficacy Trial		Tdap vs. DAPTACEL	
		n	GMC	n	GMC	GMC Ratio	95% CI
PT (EU/mL)	Pre	527	14.46	80	5.24	2.76	(2.06, 3.70)
	Post	524	309.26	80	86.55	3.57	(2.83, 4.52)
FHA (EU/mL)	Pre	527	19.49	80	5.21	3.74	(2.81, 4.99)
	Post	526	214.83	80	39.95	5.38	(4.46, 6.49)
FIM (EU/mL)	Pre	527	25.80	80	13.26	1.94	(1.52, 2.50)
	Post	526	1792.40	80	341.10	5.25	(3.90, 7.09)
PRN (EU/mL)	Pre	526	10.01	80	2.15	4.67	(3.46, 6.30)
	Post	526	344.52	80	108.12	3.19	(2.48, 4.10)

* Per-Protocol Immunogenicity Population is defined as all participants who were randomized, received assigned vaccine, and were bled to have the data according to the protocol.

Table 8: Comparison of Pertussis Antigens Between Tdap in Td506 (Adults 18-64 Years, PPI Population*) and DAPTACEL in the Sweden I Efficacy Trial

Antigens	Time	Tdap Td506 Trial		DAPTACEL Sweden I Efficacy Trial		Tdap vs. DAPTACEL	
		n	GMC	n	GMC	GMC Ratio	95% CI
PT (EU/mL)	Pre	741	12.54	80	5.24	2.39	(1.80, 3.18)
	Post	741	178.84	80	86.55	2.07	(1.58, 2.70)
FHA (EU/mL)	Pre	741	18.13	80	5.21	3.48	(2.68, 4.52)
	Post	741	192.91	80	39.95	4.83	(3.94, 5.92)
FIM (EU/mL)	Pre	741	28.56	80	13.26	2.15	(1.63, 2.84)
	Post	741	852.72	80	341.10	2.50	(1.77, 3.54)
PRN (EU/mL)	Pre	741	8.45	80	2.15	3.94	(2.89, 5.36)
	Post	741	341.89	80	108.12	3.16	(2.25, 4.44)

* Per-Protocol Immunogenicity Population is defined as all participants who were randomized, received assigned vaccine, and were bled to have the data according to the protocol.

Booster Response Rates

As per the primary hypothesis 2b that booster response rates for pertussis antigens were comparable to the booster response observed in the supportive trials with Tdap vaccine, Table 9 shows that the lower limit (LCL) of the 95% CI for booster response rate for each antigen in the PPI population is higher than the pre-defined booster rates established from the supportive studies. The acceptable booster response rates are: 81.2% for PT, 77.6% for FHA, 82.4% for FIM, and 86.4% for PRN.

Table 9: Booster Response Rates of Pertussis Antigens (PPI Population)

Antigen	Age in Years	Group	1 Month Post-Vaccination				
			M	n	%	LCL	UCL
PT (EU/mL)	11-17	Tdap	524	482	92.0	**89.3**	94.2
		Td	515	14	2.7	**1.5**	4.5
	18-64	Tdap	739	624	84.4	**81.6**	87.0
		Td	508	11	2.2	**1.1**	3.8
FHA (EU/mL)	11-17	Tdap	526	450	85.6	**82.3**	88.4
		Td	515	11	2.1	**1.1**	3.8
	18-64	Tdap	739	611	82.7	**79.8**	85.3
		Td	508	11	2.2	**1.1**	3.8
FIM (EU/mL)	11-17	Tdap	526	499	94.9	**92.6**	96.6
		Td	515	18	3.5	**2.1**	5.5
	18-64	Tdap	739	635	85.9	**83.2**	88.4
		Td	508	11	2.2	**1.1**	3.8
PRN (EU/mL)	11-17	Tdap	525	496	94.5	**92.2**	96.3
		Td	515	12	2.3	**1.2**	4.0
	18-64	Tdap	739	693	93.8	**91.8**	95.4
		Td	508	15	3.0	**1.7**	4.8

M = Number evaluated, used for calculating the percent.
n = Number of subjects with a post-/pre-titer greater than the pre-specified level.
% = n/M

Statistical Review Comments

The study protocol was revised and supplemented several times. The study power and sample size are adequate. The statistical analyses are appropriate. The results of all four primary analyses meet the pre-specified criteria. There are no major statistical issues regarding this study.

II. **STUDY Td505**

Title: "Safety and Immunogenicity of Three Lots of Tetanus and Diphtheria Toxoids Adsorbed Combined with Component Pertussis (TdcP) Vaccine in Adolescents 11-17 Years of Age"

Study Design

This was a Phase 3, randomized, controlled, double-blind, multicenter study designed to assess the safety and immunogenicity of 3 lots of Tdap vaccine when given as a booster dose in adolescents 11 to 17 years of age. Participants enrolled in the study were stratified during randomization into 2 age groups (11~13 and 14~17 years of age).

Primary Objective

To assess the lot consistency of the Tdap vaccine manufacturing process through evaluation of the immune response elicited by 3 lots when given as a booster dose.

Primary Hypothesis

The anti-pertussis [PT, FHA, FIM, PRN], anti-diphtheria toxin, and anti-tetanus toxin responses will be similar in recipients of each of 3 Tdap vaccine lots upon completion of a booster vaccination.

The following criteria were used to establish consistency of Lots 1, 2, and 3. If the two-sided 95% CIs on the difference in post-vaccination seroprotection rates and booster rates between each 2 lots were within the interval (-10%, 10%), and the two-sided 90% confidence intervals (CIs) on post-vaccination GMC ratios were within the interval (0.66, 1.5), it was concluded that the lots are consistent.

Determination of Sample Size

Planned enrollment was 1800 participants, randomized 1:1:1 to receive 1 of the 3 lots of Tdap vaccine. A total of 1170 (389 per lot) participants were to be bled for immunogenicity assessment. The sample size for the immunogenicity analysis was determined by taking 10% attrition into account such that the power for each individual hypothesis was at least 80%.

In the protocol, it was planned that statistical testing between the lots use the 90% confidence interval for the difference in rates. Following the advice of regulatory authorities and to be consistent with other studies, the 90% confidence interval was

replaced with the 95% confidence interval during the conduct of the trial. Therefore, sample size calculations for the rates are presented for both 0.05 and 0.025 α levels.

The calculation of the sample size for the immunogenicity analyses was based on the following assumptions:

1. Log (titer) for each antigen followed a normal distribution.
2. The expected proportions and GMCs for all lots were equal.
3. The lot consistency for immunogenicity was assessed by similarity criteria:
    - 95%/90% CI for difference in seroprotection rates between 2 lots
    - 90% CI for GMC Lot_i/GMC Lot_j for pertussis antigens.
4. The power to conclude consistency was calculated assuming 3 comparisons (i.e., Lot 1 vs. Lot 2, Lot 1 vs. Lot 3, and Lot 2 vs. Lot 3) for each antigen.

Tables 1 and 2 summarize information used for the sample size calculation for the immunogenicity endpoints. The sample size is 389 per each lot and 1167 for all 3 lots. All sample size calculations were determined using ---------- or in-house ---------- programs.

Table 1: Primary Endpoints, Historical Values (Targeted Response Levels) for Diphtheria, Tetanus, PT, FHA, FIM, and PRN

Antigen	Primary Endpoints	Historical Values/Targeted Response Level (95% CI)	Power [1]	
			α=0.10	α=0.05
Diphtheria IU/mL	% ≥0.10	95.0%	>99%	>99%
Tetanus IU/mL	% ≥0.10	99%	>99%	>99%
PT (EU/mL)	GMC	144 95% CI, (132, 157) N=445	>99%	---
FHA (EU/mL)	GMC	328 95% CI, (302, 356) N=446	>99%	---
FIM (EU/mL)	GMC	995 95% CI, (883, 1121) N=446	97.22%	---
PRN (EU/mL)	GMC	279 95% CI, (241, 322) N=446	83.36%	---

[1] Two-sided α.
N is the sample size used in calculating the 95% CI.

Table 2: Additional Immunogenicity Endpoints - Predicted Booster Response Rates and Predicted GMC Levels for Diphtheria and Tetanus

Antigen	Endpoint[1]	Predicted[2,3]	Power[4]	
			α=0.10	α=0.05
Diphtheria IU/mL	% booster response	92.9%	---	99%
Tetanus IU/mL	% booster response	81.6%	---	70%
Diphtheria IU/mL	GMC	7.65 95% CI (6.71, 8.72) N=326	98.79%	---
Tetanus IU/mL	GMC	26.26 95% CI (24.01, 28.72) N=326	>99%	---

[1] The pre-vaccination titer of titer ≤2.56 IU/mL for diphtheria and ≤2.7 IU/mL for tetanus represent the 95th percentile for the distribution of observed pre-vaccination titers in participants in clinical trials TC9704 and TD9805.

[2] Predicted booster response rates were estimated from the observed data from both adolescents and adults in clinical trials TC9704 and TD9805.

[3] For predicted GMC levels, only adolescent data were used.

[4] Two-sided α.

N is the sample size used in calculating the 95% CI for the predicted levels.

For the safety profile for the secondary hypothesis, using the sample size of 600 participants per lot, the power to conclude that Tdap vaccine was similar for all 3 lots was calculated for Erythema, Swelling, Pain, and Fever using the criterion that the 95% CI for the difference in response rates should be less than 10%. Table 3 summarizes sample size and power calculations for safety endpoints. The sample size for the combined Tdap lots was 1800 (600 for each lot).

Table 3: Secondary Endpoints Safety Analysis

Adverse Event	Expected Response Level[1]	Power[2]	
		α=0.10	α=0.05
Erythema	11.8%	99.96%	99.84%
Swelling	16.7%	99.33%	98.25%
Pain	88.6%	99.99%	99.88%
Fever	9.4%	99.99%	99.98%

[1] Levels obtained from clinical trial TC9704 (55), in which Tdap was given to adolescents and adults.

[2] Two-sided α.

Change in Statistical Analysis

Following the advice of regulatory authorities and to be consistent with other studies, the 90% confidence interval specified in the protocol for the statistical testing of seroprotection rates or adverse event rates between the 2 lots was replaced with the 95% confidence interval during the conduct of the trial. Also, comparisons of booster rates and

GMCs for diphtheria and tetanus were added to the immunogenicity analysis. Cut-off values used to calculate the tetanus booster response rates were revised from the original protocol to allow for EU to IU conversion as well as internal site-to-site testing concordance.

Statistical Methods

In general, the continuous variables were presented by summary statistics (i.e., mean, standard deviation, geometric mean concentrations (GMCs) and their confidence intervals) and the categorical variables by frequency distributions (i.e., frequency counts, percentages and their confidence intervals). It was assumed that log (antibody titer) for each antigen follows the normal distribution. To establish consistency among the lots, statistical testing between 2 lots by the equivalence approach was performed using two-sided 95% confidence intervals on the difference in rates and two-sided 90% confidence intervals on ratios of GMCs.

The following hypotheses were tested between any 2 lots:

For the difference between 2 proportions, at a significance level of a two-sided α=0.05:

Null Hypothesis, $H_o : | p_i - p_j | \geq \delta \quad i,j = 1,2,3, i \neq j$

Alternative Hypothesis, $H_a : | p_i - p_j | < \delta$

where δ was 10%.

For the ratio between 2 GMCs, at a significance level of a two-sided α=0.10:

Null Hypothesis, $H_o : \log GMC_i - \log GMC_j \geq \log(3/2)$

or $\log GMC_i - \log GMC_j \leq \log(2/3)$, $i,j = 1,2,3, i \neq j$

Alternative Hypothesis, H_a: $\log(2/3) < \log GMC_i - \log GMC_j < \log(3/2)$.

Confidence intervals for the outcome measures where the sample size was not justified were used only for descriptive purposes to investigate trends in the data. Baseline variables (age and gender) were compared between the study groups using the analysis of variance technique for continuous variables and the chi-square test for categorical variables. As stated above, there were 2 age strata defined in this study: 11 to 13 years and 14 to 17 years. For each age stratum, there are only descriptive comparisons between the study groups due to the insufficient sample size. In this submission, only data for combined age strata, 11 to 17 years, are analyzed.

Analysis Populations

Three analysis populations were used in this study. The intent-to-treat safety (ITTS) population included all participants who were randomized and received a Tdap vaccination. Participants who were randomized to receive one Tdap lot but received another Tdap lot were included and analyzed according to the lot they actually received. The intent-to-treat immunogenicity (ITTI) population included all participants who were randomized and received a vaccination. Note that the subset of randomized participants

who were bled for immunogenicity analysis was included in the ITTI population. The per-protocol immunogenicity (PPI) population included all ITTI participants who had no major study violations. Some participants with protocol deviations, such as a delay in the Day 4 or Day 14 telephone call, that were judged to have no impact on their immunologic response were included in the PPI population.

Immunogenicity

The statistical criterion for concluding consistency in the serology responses among the 3 lots, that supports the primary hypothesis, was based on the comparisons of GMCs for diphtheria, tetanus, and pertussis antigens and on the comparison of seroprotection rates (at a level ≥ 0.1 IU/mL) and booster rates for diphtheria and tetanus for the Per-Protocol Immunogenicity (PPI) population. Lots were determined to be consistent if the two-sided 90% confidence intervals for Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3 post-vaccination GMC ratios were within the boundaries of (0.67, 1.5) and the 2-sided 95% CIs of the difference in postvaccination seroprotection rates and booster rates between each 2 lots (Lots 1 and 2, Lots 2 and 3, Lots 1 and 3) were within the interval (–10%, 10%).

Safety

The statistical criterion for concluding consistency in the safety responses in the secondary hypothesis was based on the comparisons of Erythema, Swelling, Pain, and Fever rates Days 0-14 for the Intent-to-Treat Safety population. Per the secondary study hypothesis, if the two-sided 95% CIs on the difference between Lots 1, 2, and 3 (Lot 1 vs. Lot 2, Lot 1 vs. Lot 3, and Lot 2 vs. Lot 3) in rates of Erythema, Swelling, Pain, and Fever were within the interval (–10%, 10%), this was determined to be evidence of consistency in safety among the 3 lots with respect to these events.

Results and Conclusions

A total of 1811 participants were enrolled, of which 1791 (98.9%) completed the study. A total of 1806 randomized participants received vaccine in the Intent-to-Treat Safety (ITTS) population, and a subset of these (1175) were bled for immunogenicity assessment in the intent-to-treat immunogenicity (ITTI) population. A total of 10.1% (119/1175) participants were excluded from the per-protocol immunogenicity (PPI) population. All three groups were comparable in participant disposition (Table 4) and demographic characteristics.

Table 4: Participant Disposition

	Tdap1	Tdap2	Tdap3	Total
Randomized	603	605	603	1811
Did Not Receive Vaccine	3	1	1	5
ITTS	600	604	602	1806
Completed Study	596	599	596	1791
Discontinued Study Early	7	6	7	20
Participants with Blood Samples	393	390	392	1175
Protocol Violators	1	0	0	1
ITTI	392	390	392	1174
Protocol Violators Not in PPI	42	40	37	119
PPI	351	350	355	1056

ITTS – Intent-to-Treat Safety Population
ITTI – Intent-to-Treat Immunogenicity Population
PPI – Per-Protocol Immunogenicity Population

Comparisons of Seroprotection Rates of Diphtheria and Tetanus Toxoids

The primary hypothesis states that the anti-diphtheria toxin and anti-tetanus toxin responses will be similar in recipients of 3 Tdap vaccine lots upon completion of a booster vaccination. As part of the evaluation of lot consistency, seroprotection rates between lots of Tdap vaccine for the PPI population were compared using the 95% CI on the difference in rates between any two lots. As shown in Table 5, for both diphtheria and tetanus the 95% CIs for the differences in 1-month post-vaccination seroprotection rates (at a level of ≥0.1 IU/mL) between any 2 lots are within the interval (–10%, 10%).

Table 5: Seroprotection Rates at a Level of ≥0.1 IU/mL

Antigen	Comparison	1 Month Post Vaccination				
		Rate1 %	Rate2 %	Diff %	LCL	UCL
Diphtheria	Tdap1 vs. Tdap2	100.0	99.4	0.57	-0.22	1.36
	Tdap1 vs. Tdap3	100.0	99.7	0.28	-0.50	1.07
	Tdap2 vs. Tdap3	99.4	99.7	-0.29	-1.08	0.50
Tetanus	Tdap1 vs. Tdap2	100.0	100.0	—	—	—
	Tdap1 vs. Tdap3	100.0	100.0	—	—	—
	Tdap2 vs. Tdap3	100.0	100.0	—	—	—

Rate 1, Rate 2 : Seroprotection rates in first and second group, respectively, involved in the comparison.
Diff% : Difference between 2 lots in the proportion of participants with a titer ≥0.1 IU/mL.
LCL, UCL : Lower and upper limits of the two-sided 95% confidence interval for the difference in rates.

Comparison of Booster Response Rates of Diphtheria and Tetanus Toxoids

As part of the additional evaluation of lot consistency, booster response rates between lots of Tdap vaccine were compared for the PPI population using 95% CI on the difference in rates between any two lots. As shown in Table 6, for both diphtheria and tetanus the 95% CIs for the differences in 1-month post-vaccination booster rates between any 2 lots are within the interval (-10%, 10%).

Table 6: Comparison of Booster Response Rates

Antigen	Comparison	1 Month Post-Vaccination				
		Rate1 %	Rate2 %	Diff %	LCL	UCL
Diphtheria	Tdap1 vs. Tdap2	96.0	95.7	0.31	-2.75	3.37
	Tdap1 vs. Tdap3	96.0	94.9	1.11	-1.94	4.16
	Tdap2 vs. Tdap3	95.7	94.9	0.80	-2.25	3.86
Tetanus	Tdap1 vs. Tdap2	92.6	93.7	-1.12	-4.99	2.74
	Tdap1 vs. Tdap3	92.6	91.8	0.79	-3.06	4.64
	Tdap2 vs. Tdap3	93.7	91.8	1.91	-1.94	5.77

Rate 1, Rate 2 : Seroprotection rates in first and second group, respectively, involved in the comparison.
Diff% : Difference between 2 lots in the proportion of participants with a post-/pre-titer titer fold rise.
LCL, UCL : Lower and upper limits of the two-sided 95% confidence interval for the difference in rates.

Comparison of Geometric Mean Concentrations of Diphtheria and Tetanus Toxoids

As part of the additional evaluation of lot consistency, GMCs were compared for the PPI population between groups receiving 1 of the 3 lots of Tdap vaccine using the 90% CI on the GMC ratios between any two lots. As shown in Table 7, for both diphtheria and tetanus, the 90% CIs for the pre- and 1-month post-vaccination GMC ratios between any 2 lots are within the interval (0.67, 1.5). In addition, GMC comparisons using the 95% CI for the ratio of GMCs are also presented in Table 7 for the PPI population.

Table 7: Comparison of Geometric Mean Concentrations (GMCs) (PPI Population)

Antigen	Groups	One Month Post-Vaccination						
		GMC1	GMC2	GMC Ratio	90% CI		95% CI	
					LCL	UCL	LCL	UCL
Diphtheria	Tdap1 vs. Tdap2	7.74	7.16	1.08	0.96	1.22	0.94	1.25
	Tdap1 vs. Tdap3	7.74	7.52	1.03	0.91	1.16	0.89	1.18
	Tdap2 vs. Tdap3	7.16	7.52	0.95	0.85	1.07	0.83	1.10
Tetanus	Tdap1 vs. Tdap2	16.27	16.72	0.97	0.91	1.04	0.90	1.06
	Tdap1 vs. Tdap3	16.27	17.22	0.95	0.88	1.01	0.87	1.03
	Tdap2 vs. Tdap3	16.72	17.22	0.97	0.91	1.04	0.89	1.05

GMC1, GMC2 : GMCs for first and second group, respectively, involved in the comparison.
GMC Ratio : Ratio of GMCs for 2 groups.
LCL, UCL: Lower and upper limits of the two-sided confidence interval for the GMC ratio.

Comparison of Geometric Mean Concentrations of Pertussis

The primary hypothesis states that the anti-pertussis – PT, FHA, FIM, PRN – responses will be similar in recipients of 3 Tdap vaccine lots upon completion of a booster vaccination. As part of the evaluation of lot consistency, GMCs were compared for the PPI population between groups receiving the 3 lots of Tdap vaccine using the 90% CI on the GMC ratios between any two lots. As shown in Table 8, for PT, FHA, and PRN, the 90% CIs for the one-month post-vaccination GMC ratios between any 2 lots are within the equivalence margins (0.67, 1.5). For FIM, the 90% CIs for the one-month postvaccination GMC ratios between Lots 1 and 2 and Lots 1 and 3 in the PPI population are within the margins while the 90% CI for the GMC ratio between Lots 2 and 3, having an upper limit of 1.55, is marginally outside the margins (0.67, 1.5). In addition, the comparisons using the 95% CI for the ratio of GMCs are also presented in Table 8 for the PPI population.

Table 8: Pertussis Antigens: Geometric Mean Concentrations (PPI Population)

Antigen	Groups	One Month Post-Vaccination						
		GMC1	GMC2	GMC Ratio	90% CI		95% CI	
					LCL	UCL	LCL	UCL
PT	Tdap1 vs. Tdap2	343.65	347.36	0.99	0.87	1.13	0.85	1.16
	Tdap1 vs. Tdap3	343.65	323.89	1.06	0.93	1.21	0.91	1.24
	Tdap2 vs. Tdap3	347.36	323.89	1.07	0.94	1.22	0.92	1.25
FHA	Tdap1 vs. Tdap2	285.10	264.98	1.08	0.98	1.19	0.96	1.21
	Tdap1 vs. Tdap3	285.10	247.76	1.15	1.04	1.27	1.02	1.29
	Tdap2 vs. Tdap3	264.98	247.76	1.07	0.97	1.18	0.95	1.20
FIM	Tdap1 vs. Tdap2	1901.60	2025.38	0.94	0.80	1.10	0.78	1.13
	Tdap1 vs. Tdap3	1901.60	1528.75	1.24	1.06	1.45	1.03	1.50
	Tdap2 vs. Tdap3	2025.38	1528.75	1.32	1.13	1.55	1.10	1.60
PRN	Tdap1 vs. Tdap2	366.14	394.69	0.93	0.81	1.07	0.79	1.10
	Tdap1 vs. Tdap3	366.14	343.21	1.07	0.93	1.23	0.90	1.26
	Tdap2 vs. Tdap3	394.69	343.21	1.15	1.00	1.32	0.97	1.36

GMC1, GMC2 : GMCs for first and second group, respectively, involved in the comparison.
GMC Ratio : Ratio of GMCs for 2 groups.
LCL, UCL: Lower and upper limits of the two-sided confidence interval for the GMC ratio.

Four-Fold Response Rates of Pertussis Antigens

As part of the additional evaluation of lot consistency, four-fold response rates for the pertussis antigens one-month post-vaccination were analyzed for the PPI population. Most participants achieved four-fold rise in titer to all antigens at one-month post-vaccination: 87.4% (304/348), 80.4% (283/352), 92.5% (322/348), and 93.1% (324/348) for PT, FHA, FIM, and PRN, respectively. Table 9 shows that these rates are similar in

participants receiving Lots 1, 2, and 3. The 95% CI for the differences in 4-fold rise rates at one- month following vaccination between groups are mostly within the 10% range, except for two comparisons involving the FHA antigen.

Table 9: Comparisons of Pertussis Antigens: Four-Fold Rates

Antigen	Comparison	1 Month Post-Vaccination				
		Rate1 %	Rate2 %	Diff %	LCL	UCL
PT (EU/mL)	Tdap1 vs. Tdap2	92.0	87.4	4.67	0.06	9.28
	Tdap1 vs. Tdap3	92.0	88.1	3.95	-0.64	8.55
	Tdap2 vs. Tdap3	87.4	88.1	-0.71	-5.32	3.90
FHA (EU/mL)	Tdap1 vs. Tdap2	86.3	81.0	5.34	-0.28	10.97
	Tdap1 vs. Tdap3	86.3	80.4	5.93	0.32	11.54
	Tdap2 vs. Tdap3	81.0	80.4	0.58	-5.04	6.21
FIM (EU/mL)	Tdap1 vs. Tdap2	93.4	92.5	0.90	-2.83	4.63
	Tdap1 vs. Tdap3	93.4	93.8	-0.32	-4.04	3.39
	Tdap2 vs. Tdap3	92.5	93.8	-1.22	-4.94	2.50
PRN (EU/mL)	Tdap1 vs. Tdap2	95.4	93.1	2.34	-1.16	5.83
	Tdap1 vs. Tdap3	95.4	93.8	1.69	-1.79	5.17
	Tdap2 vs. Tdap3	93.1	93.8	-0.65	-4.14	2.84

Rate 1, Rate 2 : Seroprotection rates in first and second group, respectively, involved in the comparison.
Diff% : Difference between 2 lots in the proportion of participants with a post-/pre-titer titer fold rise.
LCL, UCL : Lower and upper limits of the two-sided 95% confidence interval for the difference in rates.

Safety Analysis: Comparison of Adverse Event Rates

The secondary hypothesis states that the Erythema, Swelling, and Pain rates will be similar between the 3 consistency lots of Tdap vaccine when given as a booster dose. To evaluate consistency between the lots, rates of Erythema, Swelling, and Pain between groups receiving the 3 different lots of Tdap vaccine were compared for 'Any' and 'Moderate & Severe' intensities for Days 0–14 using the 95% CI on the difference in rates between any 2 lots. As shown in Table 10 based on the Intent-to-Treat Safety (ITTS) Population, the 95% CIs for the differences in Erythema, Swelling, and Pain rates between any 2 lots are within the interval (–10%, 10%) for all intensity categories.

Table 10: Erythema (Redness), Swelling, and Pain: Comparison of Rates Between Groups (ITTS Population), Days 0–14

Adverse Event	Groups Compared	Any					Moderate & Severe				
		Rate 1%	Rate 2 %	Diff %	LCL	UCL	Rate 1 %	Rate 2 %	Diff %	LCL	UCL
Erythema (Redness)	Tdap1 vs. Tdap2	23.66	24.21	-0.55	-5.41	4.32	12.08	11.02	1.06	-2.55	4.68
	Tdap1 vs. Tdap3	23.66	25.08	-1.43	-6.29	3.44	12.08	11.37	0.71	-2.91	4.33
	Tdap2 vs. Tdap3	24.21	25.08	-0.88	-5.74	3.98	11.02	11.37	-0.35	-3.97	3.26
Swelling	Tdap1 vs. Tdap2	20.97	22.20	-1.23	-5.97	3.51	13.59	12.85	0.74	-3.29	4.77
	Tdap1 vs. Tdap3	20.97	24.41	-3.44	-8.18	1.30	13.59	18.06	-4.47	-8.50	-0.44
	Tdap2 vs. Tdap3	22.20	24.41	-2.21	-6.94	2.52	12.85	18.06	-5.21	-9.23	-1.18
Pain	Tdap1 vs. Tdap2	80.70	78.80	1.91	-2.64	6.45	20.97	20.87	0.11	-4.63	4.84
	Tdap1 vs. Tdap3	80.70	80.27	0.44	-4.11	4.98	20.97	25.75	-4.78	-9.52	-0.04
	Tdap2 vs. Tdap3	78.80	80.27	-1.47	-6.01	3.07	20.87	25.75	-4.88	-9.62	-0.15

Rate 1, Rate 2 :Adverse event rates for first and second groups, respectively, involved in the comparison.
Diff % : Difference in event rates between the groups being compared.
LCL, UCL : Lower and upper limits of the two-sided 95% confidence interval for the difference.
Erythema and Swelling: Any, >0 mm; Moderate & Severe, ≥10 mm.
Days 0–14: Maximum intensity of events reported during the time period.
Tdap1 (N=600), Tdap2 (N=604), Tdap3 (N=602) – Tdap Vaccine Lots C0192, C0614, and C0632, respectively, administered at Day 0.

Statistical Review Comments

The study protocol for lot consistency was revised and supplemented several times. The study power and sample size are adequate. The statistical analyses are appropriate. The results of primary analyses of immunogenicity meet the pre-specified criteria, except for a few comparisons noted above. In the safety analysis, comparisons of local adverse event rates are within the pre-specified criterion. There are no major statistical issues regarding this study.

Note that for comparisons of rates (proportions), 95% confidence intervals have been used in order to be consistent with CBER's current general statistical preference. The two-sided lot consistency comparisons involving ratios of GMCs, however, are based in this submission on 90% confidence intervals. These confidence levels, though inconsistent with CBER's current general statistical preference, may be viewed as being consistent with drug pharmacokinetic bioequivalence evaluations which are customarily based on 2-sided 90% confidence intervals. In this latter case, the alpha (significance) level is 5%, not 10%, due to the intersection-union nature of equivalence testing.