Summary Basis for Regulatory Action

Date:	April 8, 2011
From:	Rosemary Tiernan, MD, MPH Chair of the Review Committee
BLA/ STN#:	125122 / 685
Applicant Name:	Merck, Sharp and Dohme Corporation
Date of Submission: Complete Response Letter Issued: PDUFA Goal Date:	October 30, 2009 August 27, 2010 April 8, 2011
Proprietary Name/ Established Name:	RotaTeq® (rotavirus vaccine, live, oral, pentavalent)

Indication:
This supplement does not include efficacy data to support a new indication for RotaTeq. This supplement is to revise the package insert to include data from a post-marketing commitment study to evaluate safety and the risk to develop intussusception (IS) and Kawasaki disease after RotaTeq administration to infants..

Recommended Action:	Approval
Signatory Authorities Action:	Approval
Office Signatory Authority:	Wellington Sun, MD Director, DVRPA/OVRR/CBER/FDA

☐ I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

STN 125122 / 685	
Clinical Review	Thomas Buttolph, MD David Menschik, MD, MPH
Clinical Pharmacology Review	Not applicable
Statistical Review	Jingyee Kou, PhD
CMC Review (Assay)	Not applicable
Pharmacology/ Toxicology Review	Not applicable
Biomonitoring Review	Not applicable
Establishment Inspection Report	Not applicable
Advisory Committee Transcript	Not applicable
Other (list)	Not applicable

1. Introduction

This supplement contains results from a prospectively-designed observational study conducted in the USA conducted to fulfill a post-marketing commitment made at the time of approval of RotaTeq on February 3, 2006 and a revised package insert that has been updated to include these results.

RotaTeq is indicated for the prevention of rotavirus gastroenteritis caused by the G1, G2, G3 and G4 serotypes contained in the vaccine. RotaTeq is approved for use in infants 6 weeks to 32 weeks of age. The vaccination series consists of three ready-to-use liquid doses of RotaTeq administered orally starting at 6 to 12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals. The third dose should not be given after 32 weeks of age.

In order to evaluate clinical efficacy and rule out increased risk for IS after RotaTeq administration, Merck conducted a phase 3 pre-licensure trial known as the Rotavirus Efficacy and Safety Trial (REST).

The primary safety hypothesis for REST was that RotaTeq would not increase the risk of IS relative to placebo within 42 days of any dose. The statistical criteria corresponded to (1) The distribution of IS cases between vaccine and placebo groups (case split) would not reach the pre-defined safety boundary for any of the two overlapping day ranges (1 to 7 and 1 to 42 days following any dose) being monitored by the Data Safety Monitoring Board (DSMB) at any time during the trial; and (2) The upper bound of the exact 95% confidence interval estimate of the relative risk(RR) of IS at the end of the study had to be < 10.

In REST, 34,837 vaccine recipients and 34,788 placebo recipients were monitored by active surveillance to identify potential cases of IS at 7, 14, and 42 days after each dose, and every 6 weeks thereafter for 1 year after the first dose. For the primary safety outcome, cases of IS occurring within 42 days of any dose, there were 6 cases of IS among RotaTeq recipients and 5 cases among placebo recipients with RR 1.6 (95% CI 0.4, 6.4)

In the phase 3 clinical trials of RotaTeq, infants were followed for up to 42 days after a vaccine dose. Kawasaki disease was reported in 5 of 36,150 vaccine recipients and in 1 of 35,536 placebo recipients with unadjusted RR 4.9 (95% CI 0.6, 239.1).

The phase 3 studies, did not show a significantly increased risk for IS or Kawasaki disease in infants who received RotaTeq when compared to placebo. However a prospective, post-marketing observational study was conducted to further evaluate whether use of RotaTeq increased the risk to develop these serious conditions. The post-marketing study employed an independent, external Safety Monitoring Committee. The post-marketing study provided 80% power to detect a 2.5-fold increase in the IS rate over a historical rate of one per 2000 subject-years of follow-up. Among the age-group of vaccinated children, the expected background rate of IS was 50 per 100,000 person-years. [2,3,4] The study provided 66% power to detect a

3.0-fold increase in the Kawasaki Disease rate over a historical rate. The expected background rate of Kawasaki disease was 20 per 100,000 person-years.[5,6]

2. Background

This supplement was submitted on October 30, 2009. It contains a report and summary of the findings of Study 019 (Post-Marketing Evaluation of the Short Term Safety of RotaTeq). Findings from this phase 4 study were intended to satisfy the post-marketing commitment (listed in the February 3, 2006 FDA RotaTeq approval letter) to conduct a large-scale observational post-licensure safety study to evaluate the incidence of IS and other safety parameters in recipients of RotaTeq. The study utilized medical claims data from a large insured population to assess the risk of IS (primary objective) and Kawasaki Disease (added to the protocol as a secondary objective at CBER's request) based on chart-confirmed outcomes. Comparison groups included concurrent and historical (i.e., prior to RotaTeq licensure) controls who received diphtheria, pertussis, acellular pertussis vaccine (DTaP) but not RotaTeq, as well as self-controls (using a 31- 60 day post-RotaTeq vaccination window). Additionally, the study assessed risks of other health outcomes using claims data only.

A Complete Response letter (CR) was issued on August 27, 2010 in order to obtain and review the study 019 data files from ------(b)(4)------ and Merck. This SBRA will focus on safety, including statistical, review issues. There were no chemistry and manufacturing or non-clinical pharmacology toxicology issues. No clinical efficacy data were contained in this supplement.

3. Chemistry Manufacturing and Controls (CMC)

Not applicable.

4. Non-clinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology

Not applicable.

6. Clinical/Statistical

Data files from the above referenced final study report were obtained from --(b)(4)--------- with the permission and support of Merck, and reviewed jointly by the CBER Divisions of Epidemiology and Biostatistics. The study utilized medical claims data from a large insured population to assess the risk of IS (primary objective) and Kawasaki Disease (added to the protocol as a secondary objective at CBER's

request) based on chart-confirmed outcomes. Comparison groups included concurrent and historical (i.e., prior to RotaTeq licensure) controls who received DTaP but not RotaTeq, as well as self-controls (using a 31- 60 day post-RotaTeq vaccination window). Additionally, the study assessed risks of other health outcomes using claims data only.

The study population included 85,150 infants vaccinated with at least one dose of RotaTeq and 62,617 vaccinated with at least one dose of DTaP between January 2006 and December 2007 (inclusive) and followed through March 2009. Among the 85,150 infants with at least one RotaTeq vaccination, 70,998 infants received a second dose and 53,923 infants received a third dose by the end of follow-up in March 2009. For the 0-30 day follow-up window following any dose, there were 17,433 person-years among infants receiving RotaTeq and 12,339 person-years among the concurrent DTaP comparators. This follow-up time gave rise to 6 confirmed cases of IS among infants vaccinated with RotaTeq for an incidence rate of 0.3 per 1000 person-years (95% confidence interval of 0.13-0.75), compared with a background rate (based on medical literature) of 0.5 per 1,000 person-years. See Table 1 below.

There were 6 confirmed cases of IS among infants vaccinated with RotaTeq compared with 5 among the concurrent controls vaccinated with DTaP (RR = 0.8, 95% CI: 0.22-3.52). The 6 cases of IS among recipients of RotaTeq were observed after dose 1 (2 cases, days 7, 21) and dose 2 (4 cases, days 3, 6,7,8). The 5 cases of IS among the DTaP controls were observed after dose 1 (2 cases, days 12, 27), dose 2 (1 case, day 23), and dose 3 (1 case, day 4, 21). See Table 2 below.

There were 5 additional confirmed cases in the 31-60 day window (self-controls), corresponding to an incidence rate of 0.4 per 1000 person-years. Chart-confirmed findings based on comparisons with concurrent and historical DTaP controls did not support an association between immunization with RotaTeq and IS or Kawasaki Disease, with relative risks well within normal limits. Data files from the sponsor were requested to insure the accuracy of the small number of relevant outcomes.

Table 1 (from the Sponsor)

Summary of Chart-Confirmed Rates of Intussusception and Kawasaki Disease (per 1000 Person-years) Among RotaTeq Infants, Any Dose, by Follow-up Window and Comparison Cohort

Chart-Confirmed Results										
Outcome	Follow-up Window (days)	N Chart Cases	Person-years	Rate	N Chart Cases	Person-years	Rate	Relative Risk	95% Confidence Interval	
		RotaTeq Infants (n=85,150)			Concurrent DTaP Controls[1] (n=62,617)					
Intussusception	0-30	6	17,433	0.3	5	12,339	0.4	0.8	0.22 -	3.52
		RotaTeq Infants (n=85,150)			Historical DTaP Controls[2] (n=100,000)					
Intussusception	0-30	6	17,433	0.3	5	20,938	0.2	1.4	0.37 -	5.97
		RotaTeq Infants (n=85,150)			Historical DTaP Controls[3] (n=40,000)					
Intussusception	0-30	6	17,433	0.3	3	7,807	0.4	0.9	0.19 -	5.54
		RotaTeq Infants (n=85,150)			Concurrent DTaP Controls[1] (n=62,617)					
Kawasaki Disease	0-30	1	17,433	0.1	1	12,339	0.1	0.7	0.01 -	55.56

[1] Infants with DTaP vaccination in 2006 were matched to RotaTeq infants on date of birth and dose.
[2] Infants with DTaP vaccination 2001-2005.
[3] Infants with DTaP vaccination 2004-2005, last 2 years of historical control accrual.

Table 2 (from the Sponsor)

Appendix Table 10.4
Rate of Chart-Confirmed Intussusception (per 1000 Person-years) Among RotaTeq Infants versus Concurrent DTaP Controls by Dose, 1-7 Day Follow-up Window

		RotaTeq Infants (n=85,150)				Concurrent DTaP Controls[1] (n=62,617)						
Up Window (days)	Vaccine Dose[5]	N Chart Cases	Person-years	Rate	95% Confidence Interval	N Chart Cases	Person-years	Rate	95% Confidence Interval	Relative Risk[2]	95% Confidence Interval	One-Sided P Value[3]
1 - 7	Any	4[4]	4,571	0.9	0.24 - 2.24	1	3,237	0.3	0.01 - 1.72	2.8	0.28 - 139.52	0.312
	1	3	1,852	1.6	0.33 - 4.73	1	1,362	0.7	0.02 - 4.09	2.2	0.18 - 115.83	0.435
	2	1	1,545	0.6	0.02 - 3.61	0	1,084	0.0	0.00 - 2.76	∞	0.02 - ∞	0.588
	3	0	1,174	0.0	0.00 - 2.55	0	791	0.0	0.00 - 3.79			

[1] Infants with DTaP vaccination in 2006 were matched to RotaTeq infants on date of birth and dose.
[2] When both incidence rates = 0, relative risk, confidence interval, and p-value not calculated.
[3] One-sided non-midp exact probability, significant at p<0.025.
[4] Case 1: Claims Dose 1 at age 5 months (December 2006), event at Day 7 after claims Dose 1 [validation Dose 2], age 5 months; Case 2: Claims Dose 1 at age 4 months (April 2007), event at Day 6 after claims Dose 1 [validation Dose 2], age 5 months; Case 3: Claims Dose 1 at age 2 months (August 2007), event at Day 7 after claims Dose 1 [validation Dose 2], age 2 months; Case 4: Claims Dose 1 at age 2 months (December 2007), Dose 2 at age 4 months, event at Day 3 after claims Dose 2 [validation Dose 2], age 4 months.
[5] Inference by dose is limited by the small sample size of cases and exposure time in the 1-7 day follow-up window and the differing dose schedules identified in the validation of the immunization history of chart-confirmed cases of intussusception.

7. Safety Assessment

Study 019 was a phase 4 post-marketing study based on insurance claims. The methods used in this post-marketing study are acceptable. From the results presented in this supplement, the 95% confidence intervals all contained 1.0 and the upper bounds were all below 6.4, the upper bound obtained in the pivotal pre-licensure REST. Although the study results support the conclusion drawn from REST, one cannot definitively rule out a small increased risk for IS after administration of RotaTeq.

Results from this study also support the findings from REST of no significantly increased risk for Kawasaki disease in the 30 day period after administration of any dose of RotaTeq.

No other safety concerns were identified from analyses of hospitalization and emergency department visits for infants vaccinated with RotaTeq when compared to self- controls.

8. Advisory Committee Meeting

There were no issues in this supplement that required input from an Advisory Committee.

9. Other Relevant Regulatory Issues

This study had already been submitted to CBER and the firm had already been informed that they have satisfied the post-marketing commitment made at the time of RotaTeq approval. There are no other relevant regulatory issues.

10. Labeling

The final revised label was received by CBER on April 8, 2011. Revisions for the RotaTeq package insert will include the following new language:

Post-Marketing Observational Safety Surveillance Study

In a prospective post-marketing observational study conducted using a large medical claims database, the risks of intussusception or Kawasaki disease resulting in emergency department visits or hospitalizations during the 30 days following any dose of vaccine were analyzed among 85,150 infants receiving one or more doses of RotaTeq. Medical charts were reviewed to confirm these diagnoses. Evaluation included concurrent (n = 62,617) and historical (n=100,000 from 2001-2005) control groups of infants who received diphtheria, tetanus and acellular pertussis vaccine (DTaP) but not RotaTeq.

Among the age group of vaccinated children, the expected background rate of intussusception was 50 per 100,000 person-years[2,3,4] and the expected background rate of Kawasaki disease was 20 per 100,000 person-years.[5,6]

Confirmed intussusception cases within 30 days post-vaccination occurred in 6 recipients of RotaTeq (post-dose 1: day 7, 21, post-dose 2: days 3, 6, 7, 8) and 5 concurrent DTaP controls (post-dose 1: days 12, 27, post-dose 2: day 23 and post-dose 3: days 4, 21). Within 7 days of any dose, 4 recipients of RotaTeq had intussusception compared to 1 concurrent DTaP control. The relative risk of intussusception within 30 days post-vaccination among infants vaccinated with RotaTeq was 0.8 (95% CI: 0.22-3.52) compared with concurrent DTaP controls, and 1.4 (95% CI: 0.37-5.97) compared with the 2001-2005 historical control group (5 intussusception cases none occurring within 7 days of any dose),

One confirmed case of Kawasaki disease (23 days post-dose 3) was identified among infants vaccinated with RotaTeq and one confirmed case of Kawasaki disease (22 days post-dose 2) was identified among concurrent DTaP controls (relative risk = 0.7; 95% CI: 0.01-55.56).

In addition, general safety was monitored by electronic search of the automated records database for all emergency department visits and hospitalizations in the 30-day period after each dose of RotaTeq compared with: 1) days 31-60 after each dose of RotaTeq (self-matched controls) and 2) the 30-day period after each dose of DTaP vaccine (historical control subset from 2004-2005, n=40,000).

In safety analyses which evaluated multiple follow-up windows after vaccination (days: 0-7, 1-7, 8-14 and 0-30), no safety concerns were identified for infants vaccinated with RotaTeq when compared with self-matched controls and the historical control subset.

References cited in this revised section of the label

2. Davis RL, Kolczak M, Lewis E, Nordin J, Goodman M, Shay DK, Platt R, Black S, Shinefield H, Chen RT. Active surveillance of vaccine safety: a system to detect early signs of adverse events. Epidemiology 2005;16(3):336-41.
3. Kombo LA, Gerber MA, Pickering LK, Atreya CD, Breiman RF. Intussusception, infection, and immunization: summary of a workshop on rotavirus. Pediatrics 2001;108(2):E37.
4. Unpublished data from REST from the files of Merck Research Laboratories.
5. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. Pediatrics 2003;112 (3):495-501.
6. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB. Hospitalizations for Kawasaki syndrome among children in the United States, 1997-2007. Pediatr Infect Dis J 2010;29 (6):483-8.

11. Recommendations and Risk/ Benefit Assessment

Recommend: Approval of this supplement.

All members of the review team, which included staff from both the Division of Vaccines and Related Products Applications (DVRPA) and the Office of Biostatistics and Epidemiology (OBE), agreed to add the above language to the label.