

Fax - Rotarix

We are reviewing your Biologics License Application for Human Rotavirus Vaccine, Live, Oral, STN #125265/0, and we have the following comments and questions.

In regard to the Risk Management Plan, Section 2, Safety Specification:

1. We note that you refer to risk differences throughout this section. We request that you also include relative risk calculations and their respective confidence intervals in those instances where you have determined risk differences.

2. Kawasaki disease was not discussed in the safety specification. Based on the preliminary clinical review analysis of the studies **submitted in support of licensure** in the BLA, the number of Kawasaki disease cases occurring at any time interval for all doses utilized was 4 for vaccine recipients vs. 0 for placebo recipients. Of these 4 cases, two (with onset intervals of 91 and 213 days) complied with the case definitions for Kawasaki disease.

Moreover, based on the preliminary clinical review for **all** studies included in the BLA, there were two Kawasaki cases among vaccine recipients and one among placebo recipients for the 30-day period after vaccination. Although the difference found was not statistically significant, the sample size was not sufficiently large to study this important subject. Therefore, CBER believes Kawasaki disease should be discussed in the safety specification and should also be included among the outcomes to be studied in any potential post-licensure observational or active surveillance study.

3. We note that convulsions are not discussed in any detail in the safety specification. Nonetheless, in study 023, a significant difference was found for the MedDRA PT (preferred term) convulsion throughout the whole study period between vaccine and placebo groups (16 cases vs. 6, Clinical Study report, Table 25). Moreover, when a secondary analysis included other pooled codes for convulsion (table 27), the magnitude and direction of the imbalance was maintained (20 vs. 12) although, according to your analysis, the difference was no longer significant. Please confirm. Your statement that there was "no imbalance" regarding convulsion may not be accurate. If a statement regarding statistical significance is needed, it would be advisable to use more precise wording less subject to erroneous interpretation.

CBER believes that convulsion should be discussed in detail in the safety specification and should also be included among the outcomes to be studied in any potential post-licensure observational or active surveillance study.

4. In regard to intussusception, the analysis for the 31 days post-vaccination should include not only cases diagnosed within the 31 days but also, at least as a secondary analysis, all subjects with onset of intussusception within 31 days post-vaccination.

5. In regard to pneumonia deaths in study 023, you acknowledge a "potential imbalance" (page 116, following Table 37 in the body of the study report for 023) for the PT term "pneumonia" throughout the whole study period (14 deaths in the vaccine group vs. 5 in the placebo group) although by your calculations the difference was statistically significant ($p=0.040$; Table 37). In addition, in the narrative following Table 38 (last paragraph on page 117), you state that "There was no potential imbalance noted between groups for fatal SAEs related to various MedDRA PT categories for pneumonia (based on pre-defined exploratory <0.05 significance level)" when the magnitude and direction of the results was similar (16 vs. 6 subjects). On page 117 you state that this difference is not statistically significant, but this

is not in agreement with CBER's analysis, which found that the difference is significant. Please explain this discrepancy.

6. In study 036, the PT *Pneumonia* was reported significantly more in the Rotarix group compared to the placebo group from Dose 1 to Visit 7 (24 vs. 4, $p=0.029$). Of the 28 cases, only one case (Rotarix group) was reported within 31 days after vaccination. CBER's analysis shows that 3 cases in the Rotarix group compared to 0 in the placebo group reported PT Pneumonia within 43 days after vaccination. Furthermore, when the CBER reviewer combined the pneumonia-related PTs (*Pneumonia*, *Bronchopneumonia*, *Lobar pneumonia*, *Pneumonia viral*), an imbalance was still seen from Dose 1 to Visit 7 (Rotarix - 31, placebo - 7), within 31 days post-vaccination (Rotarix - 2, placebo - 0) and within 43 days post-vaccination (Rotarix - 5, placebo - 0).

Based on these findings, combined with pneumonia deaths as described above in Item #5, CBER believes that pneumonia and pneumonia fatalities within the first 43 days after vaccination (which includes days 0-42) should be examined further in any post-licensure study.

7. We note in the supplementary ISS analysis, there was a statistically significant increase for Rotarix compared to placebo recipients in the rates of the PT *Bronchitis* of any severity within 31 days post-vaccination (1.85% vs 0.74%, $RR=2.39$, 95% $CI=1.27-4.90$). Grade 3 bronchitis occurred in 6 Rotarix compared to 0 placebo recipients. You state that this imbalance was driven by an imbalance of bronchitis in the Rota-006 study. The CBER reviewer calculated a total of 41 (3.8%) Rotarix recipients (administered the less-than licensure dose) compared to 9 (1.7%) placebo recipients in Rota-006 who reported PT Bronchitis. Grade 3 bronchitis occurred in 5 Rotarix compared to 0 placebo recipients. In the core ISS analysis, when PTs *Bronchitis* and *Bronchitis acute* were combined, 116 (2.3%) Rotarix recipients and 45 (1.6%) placebo subjects reported them. Grade 3 bronchitis rates were comparable (0.16% versus 0.14%). In Rota-006, the rate of any bronchitis in the Rotarix group receiving the licensure potency dose was higher than in the placebo group (3.3% vs 1.7%); no Grade 3 bronchitis was reported in this Rotarix group.

Therefore, CBER believes that bronchitis should be included among the outcomes to be studied in any potential post-licensure observational or active surveillance study.

In regard to the Risk Management Plan, Section 3, Pharmacovigilance Plan:

8. As proposed, besides passive surveillance in the U.S. and abroad, the pharmacovigilance plan includes an active surveillance component to be implemented in Germany and the United Kingdom, and a self-controlled case-series analysis based at the Mexico Social Security network (PASS). We note that the description of the Mexico PASS study found in the BLA (dated April, 2007) does not take into account comments previously made by CBER to Dr. Judith Magner via telephone and e-mail on March 21, 2007. We hope this will be corrected in the next version of the plan. Based on the limited data provided, the studies appear large enough to address the main safety concerns, however, please provide more specific details regarding sample size and duration of the studies.

9. We have the following concerns regarding these proposed post-marketing studies:

- a. The population of Mexico is not necessarily representative of that in the U.S.
- b. The studies proposed in the U.K. and Germany, although from populations apparently socio-economically similar to the U.S., are not necessarily representative of the U.S. population.
- c. The U. K. and Germany studies are described not as prospective observational cohort

studies but as active surveillance studies. As such, they might be subject to biases and limitations common to other active surveillance studies. These may include any of the following: unverifiable completeness of reporting; unknown degree of under-ascertainment even despite a high response rate for questionnaires and cards; and lack of confirmation of case ascertainment by review of hospital discharge diagnosis.

d. All epidemiological post-licensure studies proposed are outside the U.S, and a large majority of patients studied during the clinical trials were also outside the U.S. Concerns regarding the almost total absence of U.S. data were expressed by CBER to you at the November 9, 2005 clinical development Type C meeting and at the July 17, 2006 pre-BLA meeting. During the pre-BLA meeting, CBER stated the following: "as discussed at the meeting on November 9, 2005, we have stated that a post-marketing study conducted in Mexico will not be satisfactory for post-marketing evaluation in the U.S. A post-marketing study must be conducted in the U.S. It will need to be of sufficient size to capture intussusception events and for overall safety, should be equivalent in scale to that being conducted by Merck for Rotateq®."

Because there is practically no U.S. experience with this vaccine, CBER considers it important to include a U.S. post-licensure study. It would be beneficial if the U.S. study were an observational cohort study of sufficient size to address concerns regarding intussusception. Therefore, the study should be designed to detect an increased risk of intussusception due to vaccine of 2.5 or greater with 80% probability. Other outcomes for this study should include Kawasaki disease, pneumonia, pneumonia hospitalizations, pneumonia deaths, bronchitis, and convulsions (within 60 days following vaccination). Also, it would be beneficial if, prior to implementation, there is coordination between you, the CDC and FDA to: (a) avoid duplication of efforts with CDC's Vaccine Safety Datalink study (in the initial planning stages), and (b) ensure that case definitions are compatible among studies.

10. Because of the safety signals described above, CBER proposes that the German and English studies should include also Kawasaki disease and pneumonia hospitalizations and (if feasible), pneumonia deaths among the outcomes; and that the Mexico study should include Kawasaki disease, pneumonia and bronchitis hospitalizations.

The following questions and comments are in regard to the clinical studies:

11. Rota-023

a. On page 118, Table 38 of the Rota-023 Visit 1-3 report, you calculated a p-value of 0.054 for the difference between treatment groups in deaths from pooled PTs related to pneumonia (PT Pneumonia, PT Bronchopneumonia, and PT Pneumonia cytomegalovirus). However, upon further review of the data, CBER calculated exact p-values of 0.0345 and 0.0354 using two different methodologies. Please explain the methodology by which you calculated your p-value for this SAE parameter.

b. Please provide any detailed clinical information for Subject No. 38000 regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.

12. Rota-004

a. In Study Rota-004, inclusion in the ATP efficacy cohort required that a subject had no RV other than vaccine strain in stool samples collected between the day of Dose 1 and 2 weeks post-Dose 2. Similarly, inclusion in the ATP immunogenicity cohort required that a subject

had no RV other than vaccine strain in stool samples collected from Dose 1 until Visit 3. On page 12, Table 3 of the Rota-004 Annex Report 2, you identified one subject who experienced an RV GE episode between Dose 1 and 2 weeks post-Dose 2 due to G1 wild type strain. However, based on information provided in your study report and analysis datasets, this subject did not appear to be excluded from either the ATP efficacy or immunogenicity cohorts. Please clarify.

13. Rota-006

- a. On page 128, Table 31 of your Rota-006 Year 1 study report, you indicate that one placebo recipient in the ATP immunogenicity cohort shed vaccine virus in stool collected between Day 6 to Day 10 post-Dose 2. However, on page 127, you state that "None of the placebo recipients in the ATP immunogenicity cohort shed RV, except one subject who shed wild-type G2 RV." Please clarify.
- b. On page 100, Supplement 31 of your Annex report for Rota-006, the second subheading "From Dose 1 up to the end of first efficacy period" appears to be mislabeled and should be "From Dose 1 up to the end of second efficacy period." Please clarify.
- c. On page 129, Table 33 of your Rota-006 Year 1 study report, the denominator (N) used to calculate vaccine take after Dose 1 and after Dose 2 are described as ". or with vaccine virus in stools collected after Visit 1 to Visit 2" and ".or with vaccine virus in stools collected after Visit 2 to Visit 3," respectively. This appears to be an error, as each N should include the number of subjects with available stool results during these visit intervals and not the number of subjects with vaccine virus detected in their stools. Similarly, on page 130, Table 34, you label N used to calculate vaccine take on combined Doses 1 and 2 as ". or who seroconverted at Visit 2, or with vaccine virus in stools collected after Visit 1 to Visit 3." This denominator should instead include subjects with available antibody results at Visit 2 or available stool results collected after Visit 1 to Visit 3. In your vaccine take rate tables in other study reports, you label N in a similar manner. Please clarify.
- d. Please provide any detailed clinical information for Subject No. 01650 regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.

14. Rota-007

- a. In Rota-007, please provide any detailed clinical information for Subject No. 02295 regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.

15. Rota-060

- a. On pages 55 and 56 of the initial Rota-060 Study Report, you report that 417 of the 484 total subjects completed the active phase of the study (i.e. up to Visit 6). However, on pages 30 and 31 of the Rota-060 Annex Report 1, which contained the final safety data, you report that 432 of the 484 subjects completed the extended safety follow-up phase. Please explain why more subjects completed the extended safety follow-up phase than the earlier active phase.
- b. On page 21 of the Tabular Listing of All Clinical Studies, you stated that subjects in Rota-060 were administered *Rotarix* at a potency of $10^{6.5}$ CCID₅₀ per dose. However, on page 3 and page 9 of your Rota-060 study report, you state that the vaccine composition was not

less than $10^{6.0}$ CCID₅₀. Please clarify whether a potency of $10^{6.5}$ CCID₅₀ per dose was used in Rota-060.

16. Clinical Overview

a. On page 81 of the Clinical Overview, you state that the p-value of the difference between treatment groups in deaths from pooled PTs related to pneumonia (PT Pneumonia, PT Bronchopneumonia, and PT Pneumonia cytomegalovirus) was not statistically significant ($p = 0.054$). However, as previously stated above in Comment 1 under the Rota-023 section, upon further review of the data, CBER calculated exact p-values of 0.0345 and 0.0354 using two different methodologies. Please explain the methodology by which you calculated your p-value for this SAE parameter.

b. On page 85, paragraph 3, you state that 6 cases of definite IS (1 - vaccine, 5-placebo) occurred within 31 days after Dose 1, and 7 cases (2 - vaccine, 5 - placebo) occurred within the same time period after Dose 2. These figures do not match with Table 27 on pg 84. Please clarify.

17. Efficacy Summary

a. On page 69 of the Summary of Clinical Efficacy report, you state that the exclusion criterion "Previous confirmed occurrence of RV GE" was common to all studies except Rota-023. However, this criterion was not included in the protocol for Rota-036. Please clarify.

b. On page 57 of the Summary of Clinical Efficacy, you labeled Table 18 as "Anti-HRV IgA seroconversion rates and GMCs two months after dose 2 in study Rota-007 (ATP cohort for immunogenicity)." However, on page 107 of the Rota-007 Study Report, the same seroconversion rates and GMCs were listed on line PII(M2) which meant "one month after the second dose of HRV vaccine or placebo (Visit 3)." Please clarify.

c. On page 120, Table 59 of the Summary of Clinical Efficacy Report, in the Rota-036 Spain category, the numbers of subjects (N, n) for both treatment arms and seroprotection rates for the vaccine antigens were different than corresponding figures for these same antigens in the Spain subset in Tables 36, 38, 39, and 40 in the Rota-036 Year 1 study report. Similarly, on page 121, Table 60 of the Summary of Clinical Efficacy Report, Rota-036 Spain category, the numbers (N) of subjects and anti-PT, anti-FHA, and anti-PRN GMCs for both treatment groups were different than corresponding figures for the same antigens in Table 37 of the Rota-036 Year 1 study report. Please explain the reason(s) for these differences.

18. Safety Summary

a. On page 78 of the Summary of Clinical Safety Report under the first bullet "13 cases.," you state that among intussusception cases diagnosed from Day 0-Day 30, "5 cases in the placebo group were diagnosed within 31 days after Dose 1" and "2 cases in the HRV vaccine group were diagnosed within 31 days after Dose 2." However, in Table 24 on page 76 of the same report, there were 2 cases of IS in the placebo group under the Day 0-30 post Dose 1 stratum and 5 cases of IS in the Rotarix group under the Day 0-30 post Dose 2 stratum. Please clarify.

19. Post-Marketing Report

a. On page 20, section 6.5.2 of the Periodic Safety Update Report, you state that one of the fatal cases was a 2-month-old female subject. However, on page 31 of your Risk Management Plan, you refer to this case as a 2-year-old female subject. Please clarify.

20. Risk Management Plan

a. On page 46 of your Risk Management Plan, you state that "An additional exploratory analysis showed no imbalance between treatment groups in terms of number of subjects hospitalized for pneumonia during the period from 31 days before through 31 days after each vaccine dose." However, as explained on pages 122-123 of the Rota-023 Visit 1-3 study report, analyses were conducted on pneumonia hospitalizations within 31 days and beyond 31 days after each dose. Please clarify.

21. Analysis of Kawasaki Reports Following *Rotarix*

- a. Please provide information on race for each case of Kawasaki disease from Rota-028, Rota-029, Rota-030, and Rota-061 that you reported in your Analysis. In addition, please provide the names of any routine childhood vaccinations that were administered or co-administered, the last dose number of these vaccines prior to disease onset, and interval between the last dose and disease onset. For the cases from these studies that received Rotarix, please also provide the dose potency that was administered to each of these cases.
- b. In your Analysis, you state that one placebo recipient in Rota-028 (Subject B0405862A) and one Rotarix recipient (Subject B0406754A) in Rota-030 lacked sufficient information to be classified either as Kawasaki disease or incomplete Kawasaki disease. Please provide any follow-up clinical information for these subjects regarding the diagnosis and treatment of Kawasaki disease, including reports from expert consultants, if available.
- c. On page 16, Table 4 of the Analysis, you included 30,638 Rotarix subjects and 30,527 placebo subjects for Rota-023. However, in the Rota-023 Visit 1-3 study report, you state that 31,673 Rotarix and 31,552 placebo subjects were enrolled and vaccinated, and used these figures for your safety analyses. Please explain the numerical differences between reports. Also, for each study in the Table 4, please provide the actual numbers of subjects who received at least one dose of Rotarix and placebo, respectively. Please also provide the actual exposure time in person-years for each treatment arm in each study, if available.

The following comments are in regard to the Chemistry, Manufacture and Control:

22. In your BLA, you proposed a release specification potency of ----- CCID₅₀ per dose. However, in your pivotal Phase III studies (Rota-023, Rota-036), you used a potency of 10_{6.5} CCID₅₀ per dose. You also did not use a potency of ----- CCID₅₀ per dose in your supportive efficacy studies (Rota-004, Rota-006). Furthermore, in Rota-006, efficacy estimates against any and against severe RV GE during the first year efficacy follow-up period were lower in the two lowest potency treatment arms (10^{5.3} CCID₅₀, 10^{5.6} CCID₅₀) compared to the highest potency arm (10^{6.6} CCID₅₀). Please justify the selection of your release specification potency.
23. You did not provide an ----- for the release specification potency. Please specify.
24. We note that you are using the ----- method to calculate CCID₅₀. This is not a currently recommended procedure. Please comment.
25. We note in Section 3.2.R in your BLA, that the validation reports for the potency assay dated 15 September 2003 and 30 October 2006, do not include sections addressing inter-

operator variability, an important component of precision; linearity; or accuracy. Please address these deficiencies.

The following comment applies to Amendment 0009 dated 11/15/2007 Submission m1.11.3 Efficacy Information Amendment 15 Nov 2007:

26. Regarding Figure 15 PRN ELISA: Quality Control Chart, page 11: The PRN ELISA appears to operate within the ----- limits. It was observed that between 31 Oct 2006 and 07 Nov 2006, the quality control values shifted from the lower portion of the control chart to the upper portion of the control chart. Please provide an explanation for this shift in the control chart.

Please respond to the above in an amendment to your BLA STN #125265/0. Please contact Ms. Laraine Henchal should you have any questions at 301-827-3070.