

Summary Basis for Regulatory Action

Date	March 25, 2010
From*	LCDR Jeremy L. Wally, Ph.D., Chair of the Review Committee
STN#	103606/5374
Applicant Name	Merck and Co, Inc.
Date of Submission	April 16, 2009
PDUFA Goal Date	April 26, 2010
Proprietary name	VAQTA
Indication	VAQTA is a vaccine indicated for the prevention of disease caused by hepatitis A virus (HAV) in persons 12 months of age and older.
Recommended Action	Approve the use of VAQTA administered concomitantly with varicella (ProQuad) and 7-valent pneumococcal conjugate vaccine.
Signatory Authority	Wellington Sun, M.D., Director, DVRPA

- I concur with the summary review.
 I concur with the summary review & include a separate review to add further analysis.
 I do not concur with the summary review and include a separate review.

Material Reviewed/Consulted

Specific Documentation Used in Developing the SBRA	Reviewer Name(s); Document(s) Date
Clinical Review	Nancy Miller, 2/26/10; Judy Beeler, 1/15/10
Statistical Review	Sang Ahnn, 12/15/09
Bioresearch Monitoring Review	Solomon Yimam, 1/14/10
Bioassay Reviews	Milan Blake, 1/25/10 Marian Major; 12/23/09
Label Review	Judy Beeler, Nancy Miller, Jeremy Wally, Santosh Nanda; Michael Brony, 1/20/10
Document History	Santosh Nanda, 3/22/10

*We reference the SBRA for STN 125108/341 by Judy Beeler, M.D.

1. INTRODUCTION

VAQTA is an inactivated whole virus vaccine containing hepatitis A virus adsorbed onto amorphous aluminum hydroxyphosphate sulfate. VAQTA is indicated for the prevention of disease caused by hepatitis A virus (HAV) in persons 12 months of age and older. Immunization consists of two doses given 6 to 18 months apart. The dosages are 0.5-mL for children/adolescents (12 months through 18 years of age) and 1.0-mL for adults (≥ 19 years of age). The initial dose of VAQTA should be given at least 2 weeks prior to expected exposure to HAV.

VAQTA is supplied as a sterile suspension for intramuscular injection in four presentations: 0.5-mL single-dose vials, 0.5 mL prefilled syringes, 1.0-mL single-dose vials, and 1.0-mL prefilled syringes. Each 0.5-mL pediatric dose contains approximately 25U of hepatitis A virus antigen adsorbed onto approximately 0.225 mg of aluminum. Each 1.0-mL adult dose contains approximately 50U of hepatitis A virus antigen adsorbed onto approximately 0.45 mg of aluminum.

For the single dose vial presentation, the vaccine is shaken well, withdrawn using a sterile needle and syringe, and then administered intramuscularly. For the prefilled syringe presentation, the syringe is shaken well, a sterile needle is attached, and then the vaccine is administered intramuscularly.

2. BACKGROUND

The supplement to the Biologics License Application (BLA) for VAQTA (Hepatitis A Vaccine, Inactivated) from Merck & Co., Inc., was received by CBER on April 16, 2009 and contained data to support concomitant administration of VAQTA with ProQuad (Measles, Mumps, Rubella and Varicella [Oka/Merck] Virus Vaccine Live) and 7-valent pneumococcal conjugate vaccine (Prevnar). The data submitted in support of this claim consisted of the results of Studies 066 and 067. The sponsor also submitted data from three long-term studies (Studies 023, 034 and 035) on the persistence of hepatitis A antibody following vaccination with two doses of VAQTA.

Merck had previously submitted a supplement to their BLA for ProQuad (STN 125108/341) on September 29, 2008, containing data to support concomitant immunization of ProQuad with 7-valent pneumococcal conjugate vaccine and/or VAQTA along with safety data to support the use of ProQuad as a second dose in children less than 3 years of age. Included in the supplement were the results of Studies 066 (An Open, Multicenter Study of the Safety of VAQTA and ProQuad in Healthy Children 12-23 Months of Age) and 067 (An Open, Randomized, Multicenter Study of the Safety and Immunogenicity of VAQTA Given Concomitantly with ProQuad and Prevnar in Healthy Children 12 Months of Age). This supplement has been reviewed and was approved by CBER on October 29, 2009. The sponsor has acknowledged (amendment 103606/5374.5006 of January 22, 2010) that the information submitted and

reviewed in the context of the supplement to the BLA for ProQuad also applies to the review of this supplement to the BLA for VAQTA, and has given CBER permission to cross-reference the ProQuad supplement and specified amendments in the review of the VAQTA supplement.

A BLA committee was assembled for review with an action due date of February 14, 2010. The protocol for Studies 066 and 067 were submitted and reviewed under INDs 7068 and 3152. The requested changes to the VAQTA BLA were:

- To include concomitant administration of VAQTA with varicella (ProQuad) and 7-valent pneumococcal conjugate vaccines.
- To include information on the persistence of hepatitis A antibody following vaccination with two doses of VAQTA.
- To format the package insert according to requirements identified under 21 CFR 201.57, and as outlined in the Draft Guidance for Industry: Labeling Human Prescription Drug and Biological Products-Implementing the new Content and Format Requirements.

The following table summarizes studies supporting the requested labeling changes:

VAQTA Administered Concomitantly with ProQuad and 7-Valent Pneumococcal Conjugate Vaccine				
Study	Arms (dose # in parentheses)	Number of Subjects	Immunogenicity Findings	Safety Findings Post Any Dose VAQTA
066	1) VAQTA (1) followed by VAQTA (2) ≥24 weeks post dose 1 2) VAQTA (1) + PROQUAD (1) followed by VAQTA (2) + PROQUAD (2) ≥24 weeks post dose 1	~1800	None	Fever rates (elevated >98.6°F or feverish, Days 1-14): Group 1) 16.3%, Group 2) 28.1%; Fever rates ≥100.4°F Days 1-5: Group 1) 16.3%, Group 2) 15.9%; Fever rates ≥102.2°F Days 1-5: Group 1) 4.0%, Group 2) 4.1%; Adverse event tables added (injection site adverse reactions and systemic adverse events)
067	1) VAQTA (1), ProQuad (1) & 7-valent pneumococcal conjugate vaccine (4) on Day 1; VAQTA (2) and ProQuad (2) at week ≥24; 2) ProQuad (1) 7-valent pneumococcal conjugate vaccine (4) on Day 1; VAQTA (1) at week 6, VAQTA (2) at week 30 and ProQuad (2) at week ≥34.	986	Immune responses to hepatitis A antigen 4 weeks post dose 2 were not inferior when VAQTA was given alone (dose 1 and dose 2) as compared to VAQTA(1) given with ProQuad (1) and 7-valent pneumococcal conjugate vaccine (4) and VAQTA (2) given with ProQuad (2) Immune responses to varicella antigen at 6 weeks post ProQuad (1) were not inferior when ProQuad (1) was given with 7-valent pneumococcal conjugate vaccine (4) with or without VAQTA (1) Immune responses to pneumococcal antigens were non inferior 6 weeks post 7-valent pneumococcal conjugate vaccine (4) when 7-valent pneumococcal conjugate vaccine (4) was given with ProQuad (1) with or without VAQTA (1).	Fever rates (elevated >98.6°F or feverish, Days 1-14): Group 1) 38.2%, Group 2) 18.5%; Fever rates ≥100.4°F Days 1-5: Group 1) 18.1%, Group 2) 16.7%; Fever rates ≥102.2°F Days 1-5: Group 1) 5.5%, Group 2) 3.9%; Adverse event tables added (injection site adverse reactions and systemic adverse events)
Persistence of Hepatitis A Antibody Following Vaccination with Two Doses of VAQTA				
Study	Arms (dose # in parentheses)	Number of Subjects	Antibody Persistence Findings	
023	1) VAQTA (1) followed by VAQTA (2) 6 months post dose 1 2) VAQTA (1) followed by VAQTA (2) 12 months post dose 1 3) VAQTA (1) followed by VAQTA (2) 18 months post dose 1 4) VAQTA (1) followed by VAQTA (2) 6 months post dose 1 (non-randomized) 5) VAQTA (1) followed by VAQTA (2) 6 months post dose 1*	929 (308 analyzed for persistence)	The cumulative persistence rate through ~10 years was 100% for all treatment groups. Antibody titer decreased most rapidly from 4 weeks post dose 2 to years 2.5 to 3.5, continued to decrease less rapidly through years 5 to 6, and tended to plateau from years 5 to 6 to year 10.	
034	VAQTA (1) followed by VAQTA (2) 6 months post dose 1 (healthy adults)	396 (378 included in antibody persistence analysis)	The cumulative persistence rate through ~6 years was 99.4%. Antibody titers were highest 28 weeks post dose 1, then decreased to years 2 to 3, and finally tended to plateau to year 6.	
035	VAQTA (1) followed by VAQTA (2) 6 months post dose 1 (healthy children)	325 (309 included in antibody persistence analysis)	The cumulative persistence rate through ~6 years was 100%. Antibody titers were highest 28 weeks post dose 1, then decreased to years 2 to 3, and finally tended to plateau to year 6.	

*this group original received placebo on Day 1, and were then offered VAQTA in a 0, 6-month regimen.

During the review of STN 125108/341, the review committee addressed the following review issues that are pertinent to this supplement:

- The first issue involved the reactogenicity profile observed in subjects 12 to 23 months of age given a dose of ProQuad, 7-valent pneumococcal conjugate vaccine and VAQTA concomitantly as compared with reactogenicity observed in subjects given these same vaccines at separate visits. The data from Studies 019 (An Open, Randomized, Multicenter Study to Compare Safety and Immunogenicity of ProQuad administered with Prevnar in Healthy Children 12-15 months of age reviewed by Dr. Beeler within STN 125108/341), 066 and 067 indicated that the overall reactogenicity profile of ProQuad was not significantly increased when administered concomitantly with 7-valent pneumococcal conjugate vaccine and/or VAQTA over that seen when ProQuad was administered alone. However, impact on safety of VAQTA when given alone or with ProQuad and/or pneumococcal 7-valent conjugate vaccine needed to be considered as well.

In Study 066, the rates of fever (>98.6°F or feverish) in the 14 days after vaccination were higher in subjects given any dose VAQTA + ProQuad (28.1%) as compared with subjects given any dose VAQTA alone (16.3%). In post-hoc analysis, the risk difference was 11.8% (95% CI: 6.8, 17.2) and relative risk was 1.72 (95% CI: 1.40, 2.12). The difference in rates of fever was more pronounced after VAQTA dose 1 when administered with ProQuad dose 1 (22.0%) as compared to VAQTA dose 1 alone (10.5%). After VAQTA dose 2 was administered with ProQuad dose 2, fever was reported in 12.5% of subjects, as compared to 8.5% when VAQTA dose 2 was administered alone. Rates of fever ≥100.4°F and ≥102.2°F in the 5 days after vaccination were similar in subjects who received VAQTA alone (16.3% and 4.0%, respectively) as compared to subjects who received VAQTA with ProQuad (15.9% and 4.1%, respectively). Because Study 066 did not include a ProQuad-only arm, it was not possible to determine whether the additional fevers observed in the VAQTA + ProQuad group represented an excess over that which would be expected if ProQuad were administered separately. However, the patterns of distribution of days of onset of elevated temperatures were similar in subjects who received ProQuad alone in Study 019 as compared to subjects who received VAQTA with ProQuad in Study 066.

In Study 067, the rate of fever (>98.6°F or feverish) in the 14 days after vaccination was higher in subjects given any dose of VAQTA + ProQuad dose 1 + pneumococcal 7-valent conjugate vaccine dose 4 (38.2%) as compared with subjects given any dose of VAQTA alone (18.5%). In post-hoc analysis, the risk difference was 20.0% (95% CI: 13.0, 26.8) and the relative risk was 2.10 (95% CI: 1.59, 2.79). The difference in rates of fever was more pronounced after VAQTA dose 1 when administered with

ProQuad dose 1 and pneumococcal conjugate vaccine dose 4 (35.7%) as compared to VAQTA dose 1 alone (12.4%). After VAQTA dose 2 was administered with ProQuad dose 2, fever was reported in 10.3% of subjects, as compared to 10.8% when VAQTA dose 2 was administered alone. Rates of fever $\geq 100.4^{\circ}\text{F}$ and $\geq 102.2^{\circ}\text{F}$ in the 5 days after vaccination were similar in subjects who received VAQTA alone (16.7% and 3.9%), respectively) as compared to subjects who received VAQTA with ProQuad and pneumococcal 7-valent conjugate vaccine (18.1% and 5.5%, respectively).

In the 28 days after vaccination, the administration of VAQTA dose 1 with ProQuad dose 1 and pneumococcal 7-valent conjugate vaccine dose 4 does not increase incidence rates of fever ($> 98.6^{\circ}$ or feverish) as compared to when ProQuad is administered with pneumococcal 7-valent conjugate vaccine alone (38.6% and 42.7%, respectively; relative risk 0.9 [95% CI: 0.75, 1.09] in post-hoc analysis). Similarly, the administration of VAQTA dose 2 with ProQuad dose 2 does not increase incidence rates of elevated temperatures $>98.6^{\circ}\text{F}$ as compared to when ProQuad dose 2 is administered alone (17.4% and 17.0%, respectively; relative risk 1.02 [95% CI: 0.70, 1.51] in post-hoc analysis).

Further, the pattern of distributions of days of onset of elevated temperatures were similar in subjects who received ProQuad with pneumococcal 7-valent conjugate vaccine in Study 019 as compared to subjects who received ProQuad with pneumococcal 7-valent conjugate vaccine with VAQTA in Study 067.

It was agreed that the information regarding the increased rate of fever $>98.6^{\circ}\text{F}$ or feverish in the 14 days after vaccination when ProQuad and VAQTA are administered concomitantly at 12 to 23 months of age as compared to the rate seen following VAQTA administered alone should be included in the VAQTA package insert, as well as the increased rates of fever $>98.6^{\circ}\text{F}$ or feverish in the 14 days after vaccination when ProQuad, pneumococcal 7-valent vaccine and VAQTA are administered together as compared to when VAQTA was administered alone.

All committee members agreed that the safety data indicated that ProQuad, 7-valent pneumococcal conjugate vaccine and VAQTA could be administered concomitantly and that the package insert could be modified accordingly.

- The second issue was the effectiveness of concomitant immunization with ProQuad, 7-valent pneumococcal conjugate vaccine, and VAQTA. Because Merck had previously demonstrated non-inferiority for responses to hepatitis A, measles, mumps and rubella when VAQTA and M-M-R II vaccines were administered concomitantly (in Study 057: An Open,

Randomized, Multicenter Study of the Safety and Immunogenicity of VAQTA Given Concomitantly versus Nonconcomitantly with Other Pediatric Vaccines in Children Approximately 12 Months of Age), and because the quantity of sera obtained from toddlers at each blood draw limits the number of tests that can be performed subsequently, priority was given to testing for antibody against varicella, hepatitis A, and each of the seven pneumococcal antigens. The decision was made *a priori* that it was not necessary to test for antibody to measles, mumps, and rubella in Study 067 since non-inferiority had been demonstrated in Study 057. The study design and statistical analysis plan were prospectively reviewed and approved by CBER.

All reviewers agreed that Study 067 supported Merck's findings of non-inferiority for immune response for the pre-specified endpoints of varicella, hepatitis A and for each of the seven pneumococcal antigens in children given ProQuad, 7-valent pneumococcal conjugate vaccine and VAQTA concomitantly as compared to children in the non-concomitant group given VAQTA alone followed by ProQuad and 7-valent pneumococcal conjugate vaccine 6 weeks later.

The Statistical reviewer correctly noted that the sponsor did not measure immune responses to measles, mumps, and rubella vaccine antigens in this study, and thus, no direct conclusions regarding non-inferiority of these immune responses could be made from Study 067. After full consideration of this issue, the review team recommended approval for concomitant administration of VAQTA, 7-valent pneumococcal conjugate vaccine and ProQuad, because of the data from Study 067; the supportive data from Study 057 (see above); the previous demonstration that varicella does not interfere with the immune responses to measles, mumps, or rubella antigens in ProQuad; the fact that of the antigens in ProQuad, varicella is the least immunogenic; and satisfactory immunogenicity results for this vaccine antigen were deemed to provide additional support for the inference that immune responses to the companion antigens, measles, mumps, and rubella, were also likely to be satisfactory.

This conclusion was further supported by OVRR management (Drs. Baylor, Sun, McVittie, Krause, and Pratt).

During the review of this supplement, the review committee addressed the following review issues:

- In the previously approved package insert, detectable levels of hepatitis A antibody (≥ 10 mIU/mL) were noted at 5 to 6 years post-vaccination in 99.4% (170/171) of healthy adults with geometric mean titer (GMT) of 684 mIU/mL and in 100% (174/174) of healthy children with GMT of 505

mIU/mL. Titers initially dropped, but tended to plateau from 2 to 6 years following vaccination. Previous modeling of hepatitis A antibody decay curves following administration of VAQTA indicated that, following 2 doses, antibodies would be detectable for 20 years or more in over half of the vaccinees evaluated, without additional exposure to HAV antigen. The rate of antibody decay slowed over the 2 to 3 year period post-vaccination in which antibody persistence data were available in this model.

Additional antibody persistence data following 2 doses of VAQTA is provided in this supplement for as many as 10 years, as well as statistical modeling of those data to further assess the long-term duration of antibody following vaccination with VAQTA out to 30 years. After review of the modeling information, it was determined that only the actual data of antibody persistence (out to 10 years duration) are appropriate for inclusion in the package insert. CBER communicated to Merck that modeling data were not appropriate for inclusion in the package insert in an email sent to Merck on December 18, 2009. Merck provided a response to this comment on January 25, 2010, in STN 103606/5375.5001. In that amendment, Merck agreed to the deletion of language which contained results from modeling data, and indicated that they accept the language proposed by CBER regarding the duration of immune response out to 10 years. Acceptance by the sponsor of this change to the package insert was noted in their proposed version of the package insert in that same submission.

- During a telecon of February 12, 2010, CBER and Merck were unable to come to an agreement on the language to be used in the package insert. Because review by CBER found that the information and data submitted in the SBLA were inadequate for final approval action due to ongoing discussions regarding inclusion of certain data in the package insert, a complete response letter was issued on February 12, 2010. Merck submitted a revised package insert on February 24, 2010 (amendment 103606/5374.5004). A telecon was then held between CBER and Merck on February 26, 2010, to review the package insert and agreement was reached as to the language to be used. Merck submitted a revised package insert containing the agreed upon language on March 1, 2010, in STN 103606/5374.5005. On further review, there were minor changes recommended to ensure consistency of presentation of data. These changes were accepted by Merck, and the final package insert was submitted to CBER on March 25, 2010, in STN 103606/5374.5007.

3. CHEMISTRY MANUFACTURING AND CONTROLS

The chemistry, manufacturing and quality control tests used in the release of VAQTA were not reviewed as a part of this supplement.

Review of Assays under STN 125108/341

The assays for specific pneumococcal antigens were submitted as STNs 125108/341/0 and 125108/341/1, as well as in prior submissions to INDs 7068 and 3152. The assays were reviewed and commented upon by Dr. Milan Blake. Dr. Blake concluded that the assays were acceptable for their intended use.

The assay for hepatitis A was submitted as STN 125108/341/1, with additional information submitted as STN 125108/341/3 and to IND 3152. The assay was reviewed and deemed acceptable for use in Study 067 by Dr. Marion Major.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Non-clinical pharmacology and toxicology were not reviewed as a part of this submission.

5. CLINICAL PHARMACOLOGY

Not applicable. See Clinical Review below.

6. CLINICAL/STATISTICAL

a. Background

As part of the approvals for VAQTA and ProQuad, CBER acknowledged Merck's commitment to perform three additional clinical studies to evaluate concomitant administration of VAQTA with 7-valent pneumococcal conjugate vaccine and /or ProQuad, including (1) Study 019 (Safety and Immunogenicity Study to evaluate ProQuad concomitant use with 7-valent pneumococcal conjugate vaccine, 7-Valent Conjugate Pneumococcal Vaccine), (2) Study 066 (VAQTA plus ProQuad Safety Study) and (3) Study 067 (Safety and Immunogenicity of VAQTA with ProQuad and 7-valent pneumococcal conjugate vaccine).

A brief synopsis and the main immunogenicity findings of Study 067 are given below. Safety data obtained following concomitant immunization from Studies 066 and 067 are reviewed in Section 7. Study 019 was reviewed in the ProQuad sBLA 125108/341 by Dr. Judy Beeler.

b. Clinical Review of Study 067

Provided by Dr. Nancy Miller

Title:

An open-label, randomized, multicenter study of the safety, tolerability, and immunogenicity of VAQTA given concomitantly with ProQuad and a fourth dose of 7-valent pneumococcal conjugate vaccine in healthy children 12 months of age.

Study Design:

Healthy males and females between the ages of 12 to 15 months of age with a negative clinical history of measles, mumps, rubella, varicella, or zoster who had no previous vaccination with measles, mumps, rubella, or varicella vaccines and who had written documentation that they had completed the three dose primary series of 7-valent pneumococcal conjugate vaccine, had no immune impairment, neoplastic disease, depressed immunity, or history of allergy or anaphylactoid reaction to any components in these vaccines were randomized to one of two study groups in a 1:1 ratio as follows:

- Group 1 received VAQTA dose 1, ProQuad dose 1 and 7-valent pneumococcal conjugate vaccine dose 4 concomitantly at separate injection site on Day 1 and then second doses of VAQTA and ProQuad concomitantly at separate sites at week 24 or later;
- Group 2 received ProQuad dose 1 and 7-valent pneumococcal conjugate vaccine dose 4 on Day 1, VAQTA dose 1 at Week 6, VAQTA dose 2 at Week 30 and ProQuad dose 2 at Week 34 or later.

Blood samples were drawn from all subjects just prior to vaccination on Day 1 and at about Week 6, and ≥ 4 weeks after VAQTA dose 2. Immune responses following ProQuad dose 2 were not assessed in this study because they had been evaluated in Study 057 and because the quantity of serum available for testing was limited and did not permit testing for antibody against each vaccine antigen. All subjects were followed for safety for 28 days after Visit 1, and for 28 days after ProQuad dose 2. Likewise, all subjects were also followed for 14 days following VAQTA administration including after the Week 6 visit for Groups 1 and 2 and Week 30 for Group 2 or when no vaccine was administered.

Results:

653 healthy children 12 to 15 months of age were randomized to receive VAQTA, ProQuad, and pneumococcal 7-valent conjugate vaccine concomitantly (N=330) or ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly followed by VAQTA 6 weeks later (N=323). The race distribution of the study subjects was as follows: 60.3% Caucasian; 21.6% African-American; 9.5% Hispanic-American; 7.2% other, 1.1% Asian/Pacific; and 0.3% Native American.

In the per-protocol population, the seropositivity rate to hepatitis A four weeks after a second dose of VAQTA given concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine (defined as the percent of subjects with a titer ≥ 10 mIU/mL) was non-inferior to the seropositivity rate observed when 2 doses of VAQTA were administered separately from

ProQuad and pneumococcal 7-valent conjugate vaccine (seropositivity rate difference 0.7% [95% CI: -1.4, 3.8%] and GMT fold difference 0.8 [95% CI: 0.6, 1.1]). Additionally, the GMTs for *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F 6 weeks after vaccination with pneumococcal 7-valent conjugate vaccine administered concomitantly with ProQuad and VAQTA were non-inferior as compared to GMTs observed in the group given pneumococcal 7-valent conjugate vaccine with ProQuad (the lower bounds of the 95% CI around the fold-difference for the 7 serotypes excluded 0.5).

For the varicella component of ProQuad, in subjects with baseline antibody titers <1.25 gpELISA units/mL, the proportion with a titer ≥ 5 gpELISA units/mL 6 weeks after their first dose of ProQuad was non-inferior when ProQuad was administered with VAQTA and pneumococcal 7-valent conjugate vaccine as compared to the proportion with a titer ≥ 5 gpELISA units/mL when ProQuad was administered with pneumococcal 7-valent conjugate vaccine alone (difference in seroprotection rate -5.1% [95% CI: -9.3, -1.4%]). [An earlier clinical study, Study 057, involving 617 healthy children provided data that indicated that the seroresponse rates 6 weeks post-vaccination for measles, mumps, and rubella in those given M-M-R II and VAQTA concomitantly (N=309) were non-inferior as compared to historical rates (lower bound of the 95% CI around the seroresponse rates >-10 percentage points for each antigen).]

c. Statistical Review of Study 067

Provided by Dr. Sang Ahnn (under STN 125108/341)

Primary analyses of immunogenicity were based on Per-Protocol population.

The first primary immunogenicity objective of this study was to demonstrate non-inferiority of Group 1 (VAQTA + ProQuad + 7-valent pneumococcal conjugate vaccine) to Group 2 (VAQTA administered separately from ProQuad + 7-valent pneumococcal conjugate vaccine) with respect to SPR (seropositivity rate) to hepatitis A (Table 1). The pre-specified non-inferiority margin was -10 percentage points.

Table 1. Primary Immunogenicity results [SPR* of hepatitis A 4 weeks after 2 doses of VAQTA]				
	Response Rate difference (Group1-Group2)			Non-inferiority
	Point Estimate	Lower Limit	Upper Limit	LL>-10pp
Hepatitis A	0.7	-1.4	3.8	YES

* seropositivity rate (percent ≥ 10 mIU/mL)

The second primary immunogenicity objective of this study was to demonstrate non-inferiority of Group 1 (VAQTA + ProQuad + 7-valent pneumococcal conjugate vaccine) to Group 2 (VAQTA administered separately from ProQuad + 7-valent pneumococcal conjugate vaccine) with respect to the response rates to varicella after the first dose of ProQuad (Table 2). The pre-specified non-inferiority margin was -10 percentage points.

Table 2. Primary Immunogenicity results [VZV antibody response rate 6 weeks after 1 st dose of ProQuad]				
	Response Rate difference (Group1-Group2)			Non-inferiority
	Point Estimate	Lower Limit	Upper Limit	LL>-10pp
Varicella	-5.1	-9.3	-1.4	YES

The third primary immunogenicity objective of this study was to demonstrate non-inferiority of Group 1 (VAQTA + ProQuad + 7-valent pneumococcal conjugate vaccine) to Group 2 (VAQTA administered separately from ProQuad + 7-valent pneumococcal conjugate vaccine) with respect to GMTs to each of the 7 *S. pneumoniae* serotypes (Table 3), as measured by the GMT ratio. The pre-specified non-inferiority margin was 0.5.

Table 3. Primary Immunogenicity results for [antibody responses to <i>S. pneumoniae</i> types 4, 6B, 9V, 14, 18C, 19F, and 23F 6 weeks after the 4 th dose of 7-valent pneumococcal conjugate vaccine.				
	GMT ratio (Group1/Group2)			Non-inferiority
Serotype	Point Estimate	Lower Limit	Upper Limit	LL>0.5
4	1.1	0.9	1.3	YES
6b	1.0	0.8	1.2	YES
9V	0.9	0.8	1.0	YES
14	1.0	0.9	1.2	YES
18C	1.1	0.9	1.3	YES
19F	1.1	0.9	1.2	YES
23F	1.1	1.0	1.3	YES

The statistical reviewer noted that based upon the immunogenicity data examined, a conclusion on the requested indication for concomitant use of ProQuad with Hepatitis A vaccine and Pneumococcal conjugate vaccine could not be reached, because immunogenicity data for measles, mumps, and rubella were not provided when ProQuad was concomitantly administered with Hepatitis A vaccine and Pneumococcal conjugate vaccine. This conclusion is discussed in more detail in Section 2.

d. Persistence of Hepatitis A Antibody

The sponsor provided data from three long term studies on the persistence of hepatitis A antibody following vaccination with two doses of VAQTA: Study 023 (healthy children 2 to 16 years of age), Study 034 (healthy adults 18 and older), and Study 035 (healthy subjects 2 to 17 years of age).

Previous modeling of hepatitis A antibody decay curves following administration of VAQTA indicated that, following 2 doses, antibodies would be detectable for 20 years or more in over half of the vaccinees evaluated, without additional exposure to HAV antigen. The rate of antibody decay slowed over the 2 to 3 year period post-vaccination in which antibody persistence data were available in this model. Additional antibody persistence data following 2 doses of VAQTA is provided in this supplement for as many as 10 years. These data have been reviewed and used to update duration of antibody persistence to 10 years. The sponsor also provided statistical modeling of those data to further assess the long-term duration of antibody following vaccination with VAQTA out to 30 years. However, only actual data of antibody persistence (out to 10 years duration) are appropriate for inclusion in the package insert. Results from modeling will not support claims for duration of antibody persistence to hepatitis A antigen out to 20-30 years in the package insert.

e. Results of Biomonitoring

Provided by Mr. Solomon Yimam (under STN 125108/341)

Three clinical study sites were audited. The audit at two sites revealed only minor problems with data collection. The number of errors was extremely small and would not have a significant impact on the analysis of data from this trial. There were no deviations identified during the audit of the third site.

f. Pediatrics

The data contained in this supplement do not support a new indication. Likewise, the product does not contain a new active ingredient and will not be used in a new dosing regimen, dosage form, or given using a new route of administration. The supplement does not meet the criteria specified under FDAAA PREA and further review by FDA Pediatrics Review Committee (PeRC) is not required.

g. Other Special Populations

The use of VAQTA in special populations was not considered during the review of this supplement.

7. SAFETY

a. Review of Study 066

Provided by Dr. Nancy Miller

Overview:

This was an open, multicenter study to evaluate the safety and tolerability of 2 doses of VAQTA and 2 doses of ProQuad administered at least 6 months apart to healthy children between 12 and 23 months of age, with both doses administered within that age range. All subjects received VAQTA. A subset of children received ProQuad at the same time they received VAQTA. Blinding was employed only for the assignment of randomized study treatment; once assignments were made, no blinding was in effect.

Approximately 1800 healthy subjects between 12 and 17 months of age were planned to be enrolled. The total number of subjects was first divided, without randomization, into 2 cohorts of approximately 1100 subjects and approximately 700 subjects, respectively. The 700 subjects in 1 cohort were enrolled at a subset of sites and were randomized in a 1:1 ratio to receive either 2 doses of VAQTA alone (Group 1R [Randomized]) or 2 doses of VAQTA concomitantly with ProQuad (Group 2). The remaining cohort of 1100 subjects was enrolled at different sites; these subjects were assigned to Group 1 NR [non-randomized] and were to receive 2 doses of VAQTA alone. For all subjects, the first dose of study vaccine(s) was administered on Day 1 and the second dose of study vaccine(s) was administered at least 6 months (Week 24 up to Week 51) after the first dose.

Safety follow-up was recorded and summarized after each dose of vaccine administered during the study. Temperatures were followed on Days 1 to 5 after VAQTA alone and on Days 1 to 28 following VAQTA + ProQuad, and compared based on a cut-off $\geq 102.2^{\circ}\text{F}$, [39.0°C], oral equivalent. All serious AEs and deaths were considered to be vaccine related. Safety follow-up for each group is described below:

- Group 1 (VAQTA dose 1 → VAQTA dose 2): Daily temperatures and local adverse events (pain/tenderness, redness, swelling) were recorded on Days 1 through 5; and systemic adverse events on Days 1 through 14 on a Vaccination Report Card (VRC) after each vaccination visit. Temperatures were followed Days 1 to 5. Local

adverse events and elevated temperatures were recorded for Group 1 through Day 14 in the VRC.

- Group 2 (VAQTA dose 1 + ProQuad dose 1 → VAQTA dose 2 + ProQuad dose 2): Daily temperatures and systemic adverse events Days 1 through 28; and local adverse events (pain/tenderness, redness, and swelling) on Days 1 through 5 on the VRC. Local adverse events and elevated temperatures were recorded for Group 2 through Day 28 on the VRC.

Discontinued Due to AEs:

No subject discontinued the study due to an adverse reaction.

Serious Adverse Reactions:

Overall, seven serious adverse reactions were reported by 4 subjects (3 subjects from Group 1 and 1 subject in Group 2) following any dose of VAQTA. This includes one death in Group 1 (see below) which occurred after the safety follow-up period (14 days) after VAQTA dose 2.

- Group 1 (VAQTA dose 1): Pneumonia and bacteremia 8 and 9 days after vaccination with VAQTA dose 1. This AE was not thought to be due to the vaccine administered.
- Group 1 (VAQTA dose 2): Bronchiolitis, hypoxia (12 days after VAQTA dose 2) and pneumonia (14 days after VAQTA dose 2). This AE was not thought to be due to the vaccine administered.
- Group 1 (VAQTA dose 2): A subject died following a cerebrovascular accident (stroke) that occurred 75 days after receiving a second dose of VAQTA. This event was not considered to be related to the vaccination.
- Group 2 (VAQTA dose 1 + ProQuad dose 1): Facial cellulitis and otitis media developed 18 days after immunization. This AE was considered to be possibly related to the study vaccines by the investigator.

VAQTA Injection Site Reactions (Days 1 to 5 After Any Dose of VAQTA):

The proportion reporting injection site reactions were similar in each group. At the VAQTA injection site, 49.5% in Group 1 (VAQTA alone) and 42.8% in Group 2 (VAQTA with ProQuad) reported an injection site reaction. In subjects given VAQTA alone and in those given VAQTA with ProQuad concomitantly, rates of injection site adverse reactions were lower after the second dose (35.5% and 28.4%, respectively) than after the first (36.0% and 33.5%, respectively).

Systemic Adverse Reactions (Days 1 to 14 After Any Dose of VAQTA): Systemic AEs were reported more frequently in Group 2 subjects given VAQTA and ProQuad concomitantly Days 1 to 14 after any immunization (59.0%) than in Group 1 subjects given VAQTA alone (55.3%). In subjects given VAQTA alone and in those given VAQTA with ProQuad concomitantly, systemic adverse reactions were lower after the second dose (32.6% and 34.1%, respectively) than after the first dose (42.7% and 50.9%, respectively)

Fever After Any Dose of VAQTA Alone or with ProQuad:

- Fever (>98.6°F or feverish) in the 14 days after any dose of VAQTA: Following any dose of VAQTA given alone or when given with ProQuad, fever (>98.6°F or feverish) occurred more often in Group 2 (28.1%) as compared to Group 1 (16.3%) in the 14 days after vaccination (RR 1.72, 95% CI: 1.40, 2.12).
- Fever ($\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]) days 1-5 after any dose of VAQTA: Following any dose of VAQTA alone or when given with ProQuad, fever $\geq 100.4^{\circ}\text{F}$ occurred in similar proportion in Group 1 (16.3%) and Group 2 (15.9%).
- Fever ($\geq 102.2^{\circ}\text{F}$ [$\geq 39.0^{\circ}\text{F}$]) days 1 to 5 after any dose of VAQTA: Following any dose VAQTA given alone or with ProQuad, fever $\geq 102.2^{\circ}\text{F}$ occurred in similar proportions in Group 1 (4.0%) and Group 2 (4.1%).

Fever Post-VAQTA Dose 1 Alone or with ProQuad:

- Fever (>98.6°F or feverish) in the 14 days after VAQTA dose 1: Following VAQTA dose 1 given alone or when given with ProQuad dose 1, fever (>98.6°F or feverish) occurred more often in Group 2 (22%) as compared to Group 1 (10.5%) in the 14 days after vaccination (RR 2.20, 95% CI: 1.62, 2.69).
- Fever ($\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]) days 1-5 after VAQTA dose 1: Following VAQTA dose 1 alone or when given with ProQuad, fever $\geq 100.4^{\circ}\text{F}$ occurred in similar proportion in Group 1 (11.0%) and Group 2 (12.5%).
- Fever ($\geq 102.2^{\circ}\text{F}$ [$\geq 39.0^{\circ}\text{F}$]) days 1 to 5 after VAQTA dose 1: Following VAQTA dose 1 given alone or with ProQuad, fever $\geq 102.2^{\circ}\text{F}$ occurred in similar proportions in Group 1 (2.8%) and Group 2 (3.5%).

- Fever ($\geq 102.2^{\circ}\text{F}$, oral equivalent) days 1 to 28 after vaccination: 18.2% of Group 2 subjects given ProQuad and VAQTA concomitantly experienced fever $\geq 102.2^{\circ}\text{F}$ (oral equivalent).
- Fever ($\geq 102.2^{\circ}\text{F}$, oral equivalent) days 6 to 13 after vaccination: 11.5% of subjects in Group 2 experienced fever $\geq 102.2^{\circ}\text{F}$.

[Fever data were not routinely collected beyond Day 5 after VAQTA vaccination and the study did not include a cohort given ProQuad only, so no comparisons can be made for the percent with fever Days 1-28 or Days 6-13 post-vaccination for children given ProQuad and VAQTA concomitantly to children given either VAQTA alone or ProQuad alone.]

Fever post-VAQTA Dose 2 Alone or with ProQuad:

- Fever ($>98.6^{\circ}\text{F}$ or feverish) in the 14 days after VAQTA dose 2: Following VAQTA dose 2 given alone or when given with ProQuad, fever $>98.6^{\circ}\text{F}$ or feverish occurred somewhat more often in Group 2 (12.5%) as compared to Group 1 (8.5%) in the 14 days after vaccination (RR 1.48, 95% CI: 1.02, 2.12 in post-hoc analysis).
- Fever ($\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]) days 1-5 after VAQTA dose 2: Following VAQTA dose 2 alone or when given with ProQuad, fever $\geq 100.4^{\circ}\text{F}$ occurred in similar proportions in Group 1 (8%) and Group 2 (6.8%).
- Fever ($\geq 102.2^{\circ}\text{F}$ [$\geq 39.0^{\circ}\text{F}$]) Days 1 to 5 after VAQTA dose 2: Following VAQTA dose 2 given alone or with ProQuad, fever $\geq 102.2^{\circ}\text{F}$ occurred in similar proportions in Group 1 (1.7%) and Group 2 (1.3%).
- Fever ($\geq 102.2^{\circ}\text{F}$, [$\geq 39.0^{\circ}\text{F}$]) Days 1 to 28 after vaccination: 9.2% of Group 2 subjects given ProQuad and VAQTA concomitantly experienced fever $\geq 102.2^{\circ}\text{F}$ (oral equivalent).
- Fever ($\geq 102.2^{\circ}\text{F}$, [$\geq 39.0^{\circ}\text{F}$]) Days 6 to 13 after vaccination: 3.8% of subjects in Group 2 experienced fever $\geq 102.2^{\circ}\text{F}$.

[Fever data was not routinely collected beyond Day 5 after VAQTA vaccination and the study did not include a cohort given ProQuad only, so no comparisons can be made for the percent with fever Days 1-28 or Days 6-13 post-vaccination 2 for children given ProQuad and VAQTA concomitantly to children given either VAQTA alone or ProQuad alone.]

Gastrointestinal Symptoms in the 14 Days After VAQTA:

There was a higher proportion of subjects with gastrointestinal illnesses in the 14 days after any dose of VAQTA given alone (15.5%) as compared to

when VAQTA was given with ProQuad (10.2%). The difference in proportions was small after dose 1 (9.8% in Group 1 and 7.0% in Group 2), but slightly more disparate after dose 2 (8.1% in Group 1 and 4.2% in Group 2). In a post-hoc analysis to compare proportions after dose 2, the relative risk was 1.93 (95% CI: 1.07, 3.54). For specific GI symptoms, it was found that there were a higher proportional of subjects with diarrhea in the 14 days after any dose of VAQTA given alone (10.1%) as compared to when VAQTA was given with ProQuad (6.9%). The difference in proportions was small after dose 1 (6.5% in Group 1 and 5.5% in Group 2), but slightly more disparate after dose 2 (4.9% in Group 1 and 1.9% in Group 2). In a post-hoc analysis to compare proportions after dose 2, the relative risk was 2.57 (95% CI: 1.08, 6.18). The majority of these events were mild to moderate in intensity and resolved. In this study, there was no increase in incidence of gastrointestinal symptoms or diarrhea in subjects who received VAQTA with ProQuad as compared to subjects who received VAQTA alone. Diarrhea after any dose of VAQTA is presented in the table of systemic adverse events for Study 066.

Rash:

In the 14 days after VAQTA dose 1, rashes were observed more often in subjects in Group 2 (4.0%) as compared with those in Group 1 (1.6%). Morbilliform rash was also more common in Group 2 (3.7%) than in Group 1 (0%) as expected. In the 14 days after VAQTA dose 2, rashes were observed more often in subjects in Group 2 (2.3%) as compared with dose in Group 1 (0.6%). Morbilliform rash was also more common in Group 2 (1.5%) than in Group 1 (0%).

Febrile Seizures:

One subject in Group 2 had a febrile seizure 22 days after receiving the first doses of ProQuad + VAQTA. This subject also had otitis media at the time. No febrile seizures were reported for Group 1 subjects given VAQTA alone.

Study Limitations:

Subjects given VAQTA were only followed for 14 days after vaccination for systemic adverse reactions (and only for 5 days for fever) so the data obtained for this group cannot be directly compared to reactogenicity data obtained for 28 days following concomitant vaccination with ProQuad and VAQTA. Study design did not include a ProQuad only arm for comparison. The study was an open label study and this could have contributed bias to the observations.

b. Review of Study 067
Provided by Dr. Nancy Miller

Overview:

An open, multicenter, randomized, comparative study to evaluate the immunogenicity, safety, and tolerability of the administration of VAQTA dose 1 concomitantly with ProQuad dose 1 and 7-valent pneumococcal conjugate vaccine dose 4 versus the administration of VAQTA dose 1 non-concomitantly with ProQuad dose 1 and 7-valent pneumococcal conjugate vaccine dose 4 in healthy children 12 to 15 months of age (32 sites).

This study was designed to determine whether VAQTA can be administered concomitantly with ProQuad and 7-valent pneumococcal conjugate vaccine without impairing the antibody response to any vaccine component or adversely affecting the safety profile. Currently, the fourth dose of 7-valent pneumococcal conjugate vaccine and the primary dose of measles, mumps, rubella, and varicella vaccines are typically administered between 12 to 15 months of age.

In this study VAQTA dose 1 was administered concomitantly with ProQuad dose 1 and 7-valent pneumococcal conjugate vaccine dose 4 as an investigational group and given separately from ProQuad and 7-valent pneumococcal conjugate vaccine as a control group. Safety variables for VAQTA were assessed when all 3 vaccines were administered together as compared with VAQTA administered alone.

The subjects were randomly assigned to 1 of 2 study groups in a 1:1 ratio. There were 300 subjects planned for each treatment group.

- Group 1: VAQTA dose 1 + ProQuad dose 1 + 7-valent pneumococcal conjugate vaccine dose 4 at Day 1 followed by VAQTA dose 2 + ProQuad dose 2 6 months later.
- Group 2: ProQuad dose 1 + 7-valent pneumococcal conjugate vaccine dose 4 at Day 1 followed by VAQTA dose 2 at Week 6 and Week 30, and ProQuad dose 2 at Week 34.

All subjects were followed for safety for 28 days after vaccination visits in which ProQuad was administered (Visits 1 and 3 for Group 1 and Visits 1 and 4 for Group 2), for 14 days after visits in which VAQTA was administered alone (Visits 2 and 3 for Group 2), and for 14 days following Visit 2 for Group 1. The safety follow-up period included 28 days after Visit 1 and 14 days after Visit 2 for each group, even when no vaccines were administered in Group 1, to reduce any bias which could occur if 28 days of post-vaccination follow-up in the investigational group were compared with 42 days of post-vaccination follow-up in the control group.

Injection site adverse experiences were recorded on Day 1 through Day 5 on a Vaccination Report Card, (VRC), following each vaccination visit.

Injection-site adverse events prompted for on the VRC included redness, swelling, and pain/tenderness.

Systemic adverse experiences were recorded on a VRC through Day 28 following vaccination with ProQuad, and through Day 14 following vaccination with VAQTA alone. Temperatures were followed on Days 1 to 5 after VAQTA alone and on Days 1 to 28 following VAQTA + ProQuad. Parents were instructed to record temperatures >98.6°F (>37.0°C) for Days 1 to 5 after receipt of VAQTA, but were also to report elevated temperatures or feverish feeling if they occurred through the safety follow-up period (14 days) after VAQTA. All serious AEs and deaths were considered to be vaccine related.

Discontinued Due to AEs:

One Group 2 subject discontinued the study due to an adverse reaction (GI hemorrhage secondary to a pseudo-polyp 66 days after VAQTA dose 1). This event was not thought to be related to the study vaccine.

Serious Adverse Reactions:

Eight children experienced 11 serious adverse reactions after vaccination including 2 subjects in Group 1 (given ProQuad, VAQTA and 7-valent pneumococcal conjugate vaccine concomitantly) and 6 subjects in Group 2 (Given ProQuad and 7-valent pneumococcal conjugate vaccine concomitantly and VAQTA alone).

Vaccine-Related SAEs:

Two of the serious AEs were considered to be probably or possibly vaccine related and both occurred in subjects in Group 2:

- Subject 033-028: Subject had gastroenteritis and dehydration 13 days after immunization with VAQTA dose 1 (and 55 days after vaccination with ProQuad and 7-valent pneumococcal conjugate vaccine); this illness was thought to be possibly related to immunization.
- Subject 036-006: This subject had a febrile seizure 7-9 days after ProQuad dose 1 and 7-valent pneumococcal conjugate vaccine dose 4 and subsequently had another febrile seizure 13 days after ProQuad dose 2 post-vaccination. The febrile seizures after ProQuad dose 1 were thought to be probably related to vaccination.

SAEs considered unrelated to vaccine:

- Group 1: 1 subject had pneumonia and 1 subject had cellulitis and a perineal abscess.

- Group 2: 1 subjects had genital abscess; 1 subject had a GI hemorrhage; 1 subject had gastroenteritis and dehydration; and 1 subject had bronchopneumonia.

Deaths:

None.

VAQTA Injection Site Reactions (Days 1-5 After Any Dose of VAQTA):

In the 5 days after each dose of VAQTA, the proportion of subjects with one or more injection site reaction at the VAQTA site after dose 1 was 25.4% when administered concomitantly with ProQuad and 7-valent pneumococcal conjugate vaccine and 21.5% when administered separately from ProQuad and 7-valent pneumococcal conjugate vaccine. After VAQTA dose 2, 19.8% of subjects reported at least one injection site adverse reaction at the VAQTA site when administered concomitantly with ProQuad and 25.5% when administered separately from ProQuad. Pain/tenderness was the most common injection site adverse reaction at the VAQTA injection site. There was no evidence of statistically significant differences (by relative risk or risk differences) in injection site adverse reactions in the 2 treatment groups.

ProQuad Injection Site Reactions (Days 1-5 After Any Dose of ProQuad):

In the 5 days after each dose of ProQuad, the proportion of subjects with one or more injection site reaction at the ProQuad site after dose 1 was 27.0% when administered concomitantly with VAQTA + 7-valent pneumococcal conjugate vaccine and 30.5% when administered with 7-valent pneumococcal conjugate vaccine but separate from VAQTA. After ProQuad dose 2, 21.5% of subjects reported at least one injection site adverse reaction at the ProQuad site when administered concomitantly with VAQTA and 22.2% when administered separately from VAQTA. Pain/tenderness was the most common injection site adverse reaction at the ProQuad injection site. There was no evidence of statistically significant differences (by relative risk or risk differences) in injection site adverse reactions in the 2 treatment groups.

7-Valent Pneumococcal Conjugate Vaccine Injection Site Reactions (Days 1-5 After 7-Valent Pneumococcal Conjugate Vaccine Dose 4):

In the five days after 7-valent pneumococcal conjugate vaccine dose 4 vaccination, 33.4% of subjects in Group 1 given ProQuad, 7-valent pneumococcal conjugate vaccine, and VAQTA concomitantly experienced an AE at the 7-valent pneumococcal conjugate vaccine injection site as compared with 34.2% of those in Group 2 given ProQuad and 7-valent pneumococcal conjugate vaccine concomitantly. There were no significant differences in the proportions reporting erythema, pain/tenderness, or swelling at the 7-valent pneumococcal conjugate vaccine injection site when the rates in each group were compared. The

most common injection site AE at the 7-valent pneumococcal conjugate vaccine site was pain tenderness reported in 25.7% of Group 1 and 27.9% of Group 2 but the difference was not significant (risk difference, -2.2, 95% CI, -9.2, 4.8).

Systemic Adverse Reactions:

Overall, in the 42 day cumulative safety follow-up period after Visits 1 and 2, the proportion reporting any systemic adverse reaction following any vaccination was ~63.3% in Group 1 given VAQTA+ 7-valent pneumococcal conjugate vaccine + ProQuad concomitantly as compared with 65.6% of those given VAQTA at visit 1 followed by ProQuad and 7-valent pneumococcal conjugate vaccine at visit 2. Rates of fever were compared at different cut-off points ($>98.6^{\circ}\text{F}$ [$>37.0^{\circ}\text{C}$], $\geq 100.4^{\circ}\text{F}$ [$\geq 39.0^{\circ}\text{C}$], and $\geq 102.2^{\circ}\text{F}$ [$\geq 39.0^{\circ}\text{C}$]) between treatment groups when follow-up periods were 5 days in length, 14 days in length, and 28 days in length. These different analyses are described below. No other clinically significant differences in systemic adverse reactions were reported among treatment groups in the 42 day cumulative follow-up period.

Fever After Any Dose of VAQTA When Given Alone or with ProQuad and 7-Valent Pneumococcal Conjugate Vaccine:

- Fever ($>98.6^{\circ}\text{F}$ or feverish) in the 14 days after any dose of VAQTA: Following any dose of VAQTA given alone or when given with ProQuad dose 1 and pneumococcal 7-valent conjugate vaccine dose 4 or with ProQuad dose 2, fever $>98.6^{\circ}\text{F}$ occurred more often in Group 1 (38.2%) as compared to Group 2 (18.5%) in the 14 days after vaccination (RR 2.10, 95% CI: 1.59, 2.79).
- Fever ($\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]) days 1-5 after any dose of VAQTA: Following any dose of VAQTA alone or when given with ProQuad dose 1 and pneumococcal 7-valent conjugate vaccine dose 4 or ProQuad dose 2, fever $\geq 100.4^{\circ}\text{F}$ occurred in similar proportions of subjects in Group 1 (18.1%) as compared to Group 2 (16.7%).
- Fever ($\geq 102.2^{\circ}\text{F}$ [$\geq 39.0^{\circ}\text{C}$]) days 1 to 5 after any dose of VAQTA: Following any dose of VAQTA given alone or with ProQuad dose 1 and pneumococcal 7-valent conjugate vaccine dose 4 or ProQuad dose 2, fever $\geq 102.2^{\circ}\text{F}$ occurred in similar proportions in Group 1 (5.5%) and Group 2 (3.9%).

Fever Post-VAQTA Dose 1 Alone or with ProQuad and 7-Valent Pneumococcal Conjugate Vaccine:

- Fever ($>98.6^{\circ}\text{F}$ or feverish) in the 14 days after VAQTA dose 1: Following VAQTA dose 1 given alone or when given with ProQuad

and pneumococcal 7-valent conjugate vaccine, fever >98.6°F occurred more often in Group 1 (35.7%) as compared to Group 2 (12.4%) in the 14 days after vaccination (RR 2.9, 95% CI: 2.0, 4.1).

- Fever ($\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]) days 1-5 after VAQTA dose 1: Following VAQTA dose 1 alone or when given with ProQuad and pneumococcal 7-valent conjugate vaccine, fever $\geq 100.4^{\circ}\text{F}$ occurred in a higher proportion of subjects in Group 1 (16.8%) as compared to Group 2 (10.3%).
- Fever ($\geq 102.2^{\circ}\text{F}$ [$\geq 39.0^{\circ}\text{F}$]) days 1 to 5 after VAQTA dose 1: Following VAQTA dose 1 given alone or with ProQuad, fever $\geq 102.2^{\circ}\text{F}$ occurred in similar proportions in Group 1 (2.8%) and Group 2 (3.5%).

Fever Post-VAQTA Dose 2 Alone or with ProQuad:

- Fever (>98.6°F or feverish) in the 14 days after VAQTA dose 2: Following VAQTA dose 2 given alone or when given with ProQuad, fever >98.6°F occurred in similar proportions in Group 2 (10.8%) as compared to Group 1 (10.3%) in the 14 days after vaccination (RR -0.5, 95% CI: -5.8, 4.9 in post-hoc analysis).
- Fever ($\geq 100.4^{\circ}\text{F}$ [$\geq 38.0^{\circ}\text{C}$]) days 1-5 after VAQTA dose 2: Following VAQTA dose 2 alone or when given with ProQuad, fever $\geq 100.4^{\circ}\text{F}$ occurred in a slightly higher proportion of subjects in Group 2 (10%) as compared to Group 2 (4.2%).
- Fever ($\geq 102.2^{\circ}\text{F}$ [$\geq 39.0^{\circ}\text{F}$]) days 1 to 5 after VAQTA dose 2: Following VAQTA dose 2 given alone or with ProQuad, fever $\geq 102.2^{\circ}\text{F}$ occurred in similar proportions in Group 1 (2.5%) and Group 2 (2.3%).

Gastrointestinal Symptoms in the 14 Days After VAQTA:

There was a slightly higher proportion of subjects with gastrointestinal illnesses in the 14 days after any dose of VAQTA when given with ProQuad dose 1 and pneumococcal 7-valent conjugate vaccine dose 4 or with ProQuad dose 2 (8.2%) as compared to when VAQTA was given alone (4.9%). The difference in proportions was higher in the concomitant group after dose 1 (7.1% in Group 1 and 2.6% in Group 2), but more similar after dose 2 (2.7% in Group 1 and 3.2% in Group 2). In a post-hoc analysis to compare proportions after dose 1, the relative risk after was 2.77 (95% CI: 1.23, 6.26). For specific GI symptoms, there was a higher proportion of subjects with diarrhea in the 14 days after any dose of VAQTA given alone (2.8%) as compared to when VAQTA was given with ProQuad and pneumococcal 7-valent conjugate vaccine (4.8%). The

difference was larger after dose 1 (4.2% in Group 1 and 1.1% in Group 2), but more similar after dose 2 (1.5% in Group 1 and 2.0% in Group 2). In a post-hoc analysis to compare proportions after dose 1, the relative risk was 3.82 (95% CI: 1.18, 13.42). The majority of these events were mild to moderate in intensity and resolved. In Study 067, there was a slightly higher incidence of gastrointestinal symptoms or diarrhea in subjects who received VAQTA dose 1 with ProQuad dose 1 and pneumococcal 7-valent conjugate vaccine dose 4 as compared to subjects who received VAQTA dose 1 separate from the other vaccines. It is noted that 2 subjects had serious adverse events after receipt of VAQTA dose 1 or VAQTA dose 2 alone (not concomitant with other vaccines), and one was considered possibly related to vaccine. Diarrhea after any dose of VAQTA is presented in the table of systemic adverse events for Study 067.

Rashes:

In the 42 days after vaccination, 5.3% of children given ProQuad dose 1 + 7-valent pneumococcal conjugate vaccine dose 4 in Group 2 experienced measles-like rashes after vaccination as compared with 3.3% of children given ProQuad dose 1 + 7-valent pneumococcal conjugate vaccine dose 4 + VAQTA dose 1 in Group 1.

Febrile Seizures:

Three subjects experienced four febrile seizures in this study with one subject in each arm. One Group 1 subject experienced a febrile seizure 9 days following vaccination with ProQuad dose 1, 7-valent pneumococcal conjugate vaccine dose 4, and VAQTA dose 1. One subject in Group 1 experienced a febrile seizure 25 days after receipt of ProQuad dose 2 and VAQTA dose 2. One subject in Group 2 experienced febrile seizures 9 days after ProQuad dose 1 and 7-valent pneumococcal conjugate vaccine dose 4 vaccination and then again 13 days after vaccination with ProQuad dose 2.

Study Limitations:

It must be noted that rates of adverse reactions were compared for the entire 42 day period in which vaccines were given concomitantly as compared to those who received study vaccines non-concomitantly, which may dilute differences between the concomitant and non-concomitant groups.

Study 067 did not include a group of children randomized to receive ProQuad alone. Although there appears to be a trend toward an increase in fevers days 1 to 28 after vaccination in children given ProQuad + 7-valent pneumococcal conjugate vaccine + VAQTA (21.3%) in Study 067 as compared with subjects given ProQuad alone (14.7%) in Study 019, statistical comparisons of reactogenicity cannot be made across studies. Further different definitions of fever were used in these two studies

(>98.6°F or feverish in Study 067 and \geq 101.0°F in Study 019). Similarly, there appears to be about a 50% increase in fevers reported days 6 to 13 after vaccination when the rate in subjects given ProQuad + 7-valent pneumococcal conjugate vaccine + VAQTA (16.0%) is compared with the rate reported for subjects given ProQuad alone (10.6%, Study 019). However, there were no other apparent and consistent increases in local or systemic reactogenicity seen in subjects as the number of vaccines administered concomitantly with ProQuad was increased.

The studies were open-label studies and this could have contributed bias to the observations.

8. ADVISORY COMMITTEE MEETING

CDER did not present these data to an Advisory Committee.

9. OTHER RELEVANT REGULATORY ISSUES

There were no other relevant regulatory issues discussed during the review of this supplement.

10. LABELING

a. Package Insert

A review of the package insert was submitted by Michael Brony of APLB. All substantive changes in format recommended by the APLB review were incorporated into the revised label.

The label was revised using the format recommended under the requirements identified under 21 CFR 201.57, and as outlined in the Draft Guidance for Industry: Labeling Human Prescription Drug and Biological Products-Implementing the new Content and Format Requirements.

Subsequent labeling discussions were held with the sponsor. All labeling issues have been adequately resolved.

b. Carton and Immediate Container Labels

The carton and immediate container labels were not reviewed as a part of this supplement as no changes were made to these labels.

c. Patient Labeling/Medication Guide:

The patient labeling/medication guide was not reviewed as a part of this supplement.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a. Recommended Regulatory Action:

The committee recommends approval of a package insert change to indicate that VAQTA may be administered concomitantly with 7-valent pneumococcal conjugate vaccine and varicella (ProQuad) based on the data provided in Study 067. The committee recommends inclusion of statement regarding duration of hepatitis antibody of 10 years' duration (based on GMTs of anti-hepatitis A antibody).

b. Risk/ Benefit Assessment

Safety and efficacy of this vaccine have been reviewed and have been determined to be acceptable for use of this vaccine as indicated in the label.

c. Recommendation for Post-marketing Risk Management Activities

No post-marketing risk management activities are recommended for this supplement.

d. Recommendation for Post-marketing Activities

Routine post-marketing passive surveillance of adverse events will continue; additional post marketing activities specific to this supplement are not recommended.