Summary Basis for Regulatory Action

Date: July 21, 2011

From: Nancy Miller, M.D., Clinical Reviewer and Review Committee Chair

BLA/STN: 103475/5343

Applicant Name: GlaxoSmithKline Biologicals

Date of Submission: 9/23/10 and 10/19/10

PDUFA Goal Date: July 24, 2011

Proprietary/ Established Name:
Havrix
Hepatitis A Vaccine

Indication and Usage:
For use in children ≥ 12 months of age
For active immunization for against disease caused by hepatitis A virus (HAV).

Recommended Action: APPROVAL

Signatory Authorities Action: Wellington Sun, M.D.
Director, Division of Vaccines and Applied Product Applications

Office's Signatory Authority:

√ 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.

Material Reviewed/ Consulted Reviewer Name – Document(s) Date	**Specific documentation used in developing the SBRA**
Clinical Review	Nancy Miller, M.D. – 6/6/11
Statistical Review	Lihan Yan, Ph.D. – 6/3/11
Serological Immune Response Assay Review/CMC Hepatitis A Measles, mumps and rubella Varicella	 Marion Major, Ph.D. – 4/13/11 Steve Rubin, Ph.D. 10/29/10; 2/7/11 Shuang Tang, Ph.D. – 4/19/11
Advertising and Promotional Labeling	Michael Brony -
Biomonitoring Bioresearch Monitoring Review	Bhanu Kannan -

In addition to the review documents listed above, records of meeting summaries and teleconferences, as well as e-mails exchanged internally and with the applicant were referenced.

1. Introduction

Supplemental Biologics License Application (sBLA) 103475/5343 is submitted by GlaxoSmithKline Biologicals (GSK) to fulfill two post-marketing commitments as noted in the approval letter for Havrix dated 10/17/05, in which the lower age of administration of Havrix was changed from ≥ 2 years to ≥ 12 months of age. Clinical data was submitted to support the co-administration with measles, mumps and rubella vaccine (MMRII) and varicella vaccine (Varivax) as noted in Post-Marketing Commitment #3 in the 10/17/05 approval letter. In addition, safety data for HAV-231, along with safety data from 3 other previously submitted studies (HAV-210, HAV-220 and HAV-232) was submitted to support safety in at least 3000 children in the second year of life to fulfill Post-Marketing Commitment #1.

The following major issues relevant to the review of sBLA 103475/5343, are discussed in this document:

a. Validation of assays to assess serological responses to hepatitis A (HAV), measles, rubella, mumps (MMRII) and varicella antigens (Varivax). The data provided adequately validated these assays for the purpose of evaluating the concomitant administration of Havrix with measles, mumps, rubella and varicella vaccines.
b. The pre-specified criteria for non-inferiority were met for all antigens (hepatitis A, measles, mumps, rubella, and varicella).
c. Revised definitions for serological responses to demonstrate non-inferiority of mumps, measles, and varicella when MMRII and Varivax are coadministered with Havrix as compared to when MMRII and Varivax are given without Havrix were employed in post-hoc analyses. These revised definitions were considered more clinically relevant for measles (<150 mIU/mL at pre-vaccination to ≥200 mIU/mL post-vaccination) and mumps (< 1:24 pre-vaccination to ≥51 post-vaccination). For varicella antigen, the assay used (----------(b)(4)----------) employed a cut-off of seropositivity of ≥ 40 1/DIL. Seroresponse was defined as a 4-fold increase in anti-varicella titer. Using the revised definitions for seroconversion to measles and varicella antigens, the immune responses to measles and varicella antigens were again non-inferior in the concomitant group (HAV+MMRII+V) as compared to when MMRII and Varivax were administered without HAV (MMRII+V→HAV group). Using the more stringent definition for immune response to mumps antigen, however, non-inferiority to mumps antigen when Havrix was administered with MMRII and V as compared to MMRII+V followed by Havrix was not demonstrated. Because differences in immune responses to mumps antigen in the two dosing regimens were small, and considering that the study was not powered adequately for the revised definition, it is unlikely that concomitant administration of HAV with MMRII and Varivax results in clinically meaningful interference in immune response to mumps antigen.

2. Background

Product Description
Havrix is a sterile suspension of inactivated virus. The virus (strain HM175) is propagated in MRC-5 human diploid cells. Each 1-mL adult dose of vaccine contains 1440 EL.U. of viral antigen, adsorbed on 0.5 mg of aluminum as aluminum hydroxide. Each 0.5-mL pediatric dose of vaccine contains 720 EL.U. of viral antigen, adsorbed onto 0.25 mg of aluminum hydroxide. Havrix contains the following excipients: Amino acid supplement (0.3% w/v) in a phosphate-buffered saline solution and polysorbate 20 (0.05 mg/mL). From the manufacturing process, Havrix also contains residual MRC-5 cellular proteins (not more than 5 μg/mL), formalin (not more than 0.1 mg/mL), and neomycin sulfate (not more than 40 μg/mL), an aminoglycoside antibiotic included in the cell growth media. Havrix is available in vials and 2 types of prefilled syringes. One type of prefilled syringe has a tip cap which may contain natural rubber latex. The other type has a tip cap and a rubber plunger which contain natural latex rubber. The vial stopper does not contain latex.

Regulatory History
Havrix is a vaccine indicated for active immunization against disease caused by hepatitis A virus (HAV) for persons ≥ 12 months of age. Havrix was initially licensed in persons ≥ 2 years of age in the Unites States (U.S.) in 1995. The protective efficacy and safety were evaluated in a controlled study involving 40,119 children 1-16 years of age in Thailand at high risk for hepatitis infection. The presence of antibody to hepatitis A is considered a demonstration of protection against hepatitis A disease. The age indication was extended to children as young as 12 months of age in 2005, based on demonstration of non-inferiority of immune response in children 12-23 months of age as compared to children 23-25 months of age (HAV-210). At the time the age indication was extended to children as young as 12 months of age (10/17/05), GSK agreed to evaluate the safety of administering two doses of Havrix six months apart in at least 3000 children 12 to 23 months of age. Three coadministration studies were specified as post-marketing commitment studies in that approval letter: 1) a study to evaluate the safety and immunogenicity of Havrix when administered with or without pneumococcal 7-valent conjugate vaccine (diphtheria CRM 197 protein) [Prevnar]; 2) safety and immunogenicity of Havrix when administered with or without diphtheria, tetanus toxoids, and acellular pertussis vaccine, adsorbed [Infanrix] and haemophilus b conjugate vaccine (tetanus toxoid conjugate) [ActHIB]; and 3) the safety and immunogenicity of Havrix when administered with or without measles, mumps, and rubella vaccine (MMRII) and varicella vaccine (Varivax). The first two studies were previously submitted to the Havrix BLA as efficacy supplements, and resulted in the addition of data to the package insert (PI) for coadministration of Havrix with Prevnar (approved 3/26/08) , and addition of data to the PI for coadministration of Havrix with Infanrix and ActHIB (approved 10/1/09).

With this supplement, GSK submitted the third of three post-marketing commitment studies (HAV-231) to the BLA to provide safety and immunogenicity data which support

coadministration of Havrix with MMRII and Varivax in children in the second year of life.

The second part of this supplement includes pooled safety data from four studies (HAV-210, HAV-220, HAV-232 and HAV-231), assessing safety and immunogenicity of Havrix given with or without concomitant childhood vaccines in at least 3000 children in the second year of life. These pooled safety data will be included in the package insert and will replace the individual safety data for each of the other three studies.

3. Chemistry Manufacturing and Controls (CMC)-Serology Assay Reviews

There were no changes in product within this supplemental BLA.

Full CMC review of Havrix was initially completed at the time of original licensure in 1995. Over the ensuing years, all lots of vaccine used in the concomitant study were reviewed and released for distribution by CBER.

The CMC reviews focused on the assays used to evaluate the immune response to each of the antigens included in the vaccines administered in the study. Because assessment of potential diminution of the immune response was one of the primary goals of the study, validation of the serology assays was a critical and essential part of the review of this supplement.

The assays for the serological responses to five separate antigens were considered. Separate reviews were performed for the immune response assay for each of the following sets of antigens:

1. Hepatitis A: Antibody response to hepatitis A was determined by ---(b)(4)--- ELISA assay and---(b)(4)--- ELISA assay. The current Standard Operating Procedure (SOP) was reviewed and found to be acceptable, and the validation of the assay to detect antibodies to HAV in clinical samples was previously reviewed and found to be acceptable.
2. Measles: Enzyme immunoassay for the qualitative and quantitative determination of IgG antibodies to measles virus in human serum and plasma and performance characteristics and validation was utilized to measure immune response to measles. Anti-measles antibodies were measured using commercially purchased ----------(b)(4)------ ELISA kit. While the assay was assessed as adequately validated for operating characteristics for use in this coadministration study, their use in assessment of vaccine immunogenicity was problematic given an update in definition of measles seroconversion. The original definition of seroresponse to measles in study HAV-231 (2003-4) was defined as a change in seronegative subject (<150 mIU/mL pre-vaccination) to a post-vaccination measles antibody titer of ≥ 150 mIU/mL). Based on subsequent discussions with GSK in the context of another IND in late 2007, measles seroresponse was defined as change in antibody concentration ≥ 200 mIU/mL at 42 days after vaccination with MMRII, a level of antibody associated with protection in seronegative subjects (<150

3. Rubella: Enzyme immunoassay for the qualitative and quantitative determination of IgG antibodies to rubella virus in human serum and plasma and performance characteristics and validation was utilized to measure immune response to rubella. The anti-rubella antibodies were measured using commercially purchased -------(b)(4)------- ELISA kits. This assay was assessed as acceptable for use in this coadministration study.
4. Mumps: Mumps virus ----------(b)(4)---------- was utilized to measure immune response to mumps. The pre-specified definition of seroconversion to mumps antigen (< 1:28 titer pre-vaccination to ≥ 1:28 titer at 42 days after vaccination with MMRII) was not considered adequate for definition of seroresponse to MMRII. Recommendations had been provided to the sponsor again in late 2007 to calculate the immune response to mumps antigen as a change from <1:24 titer pre-vaccination to a titer ≥ 1:51 at 42 days post-vaccination. Although the pre-specified criterion for non-inferiority in immune response to mumps antigen was met, the post-hoc analysis did not demonstrate non-inferiority. Differences in immunogenicity between the two vaccine regimens (concomitant versus non-concomitant administration of Havrix, MMRII and Varivax) were small, however, and the interpretation of these data were limited due to the study not being adequately powered for the definition used in the re-analysis. In light of these considerations, concomitant administration of HAV with MMRII and Varivax appears unlikely to interfere with protection against mumps in this population. Please see clinical discussion for further assessment of the results.
5. Varicella: ----------(b)(4)---------- was used to determine immune response to varicella zoster virus. The ----------(b)(4)---------- test of Varicella Zoster virus (VZV), and was performed in ----------(b)(4)----------. The originally agreed upon definition of seroresponse to varicella (titer < 5 pre-vaccination to titer ≥ 5 post-vaccination) was revised to define response as a change in titer from < 40 1DIL pre-vaccination to a 4-fold increase in titer at 42 days post-vaccination with Varivax. Both pre-specified and post-hoc analyses demonstrated non-inferiority of immune response to varicella antigen and support the conclusion that there is no interference in anti-varicella immune responses when Havrix was administered with MMRII and Varivax as compared to when MMRII and Varivax was administered 42 days prior to administration of Havrix.

4. Preclinical Pharmacology/Toxicology

Not applicable.

5. Clinical (Immunogenicity and Safety)

Two datasets were considered in the review of this supplement. The first dataset involved review of study HAV-231 for assessment of immunogenicity and safety of administering

the Havrix alone, Havrix dose 1 concomitantly administered with MMRII and Varivax, or Havrix dose 1 administered at 42 days after MMRII and Varivax given together. The second dataset assessed the combined safety profile of Havrix administered alone as compared to concomitant administration with other childhood vaccines in studies HAV-210, HAV-220, HAV-232, and HPV-231. Study HAV-210 supported approval of Havrix administration in children as young as 12 months of age [October 17, 2005]; study HAV-220 supported coadministration of Havrix with Prevnar in children during the second year of life [March 26, 2008]; and study HAV-232 supported coadministration of Havrix with DTaP (Infanrix) and Hib (ACTHib) vaccines in children during the second year of life [October 1, 2009]. Taken together with study HAV-231 in the present supplement, safety data was provided in more than 3000 children 12-23 months of age, and fulfills the remaining post-marketing commitments which were stipulated in the approval letter of October 17, 2005. The previous approval letters and supporting documents can be found at the following FDA website:
http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm110016.htm.

STUDY HAV-231

Study (HAV-231) was a randomized, controlled, open label, multicenter, safety and immunogenicity trial of concomitant use of Havrix with MMRII and varicella vaccine (Varivax). Three groups (randomized) were included in the study: one group received Havrix alone at Month 1 and Month 6; one group received Havrix concomitantly with MMRII and Varivax, followed 6-9 months later by the 2nd dose of Havrix; and the third group received MMRII with Varivax at Month 0, followed 42 days by dose 1 Havrix, followed 6-9 months after dose 1 Havrix with dose 2 Havrix. Each dose of Havrix was administered in the left thigh, and MMRII and Varivax administered in the deltoid muscles of opposite arms. Please see Table 1 for the treatment groups and times of vaccine administration.

Table 1: Study HAV-231 – Vaccine Administration

Group	Vaccine	Dose	Visit (Time point)	Route	Site	Side
HAV	Havrix	1 2	2 (Day 0) 4 (Month 6-9)	IM	Thigh	Left
HAV+MMR+V	Havrix	1 2	2 (Day 0) 4 (Month 6-9)	IM	Thigh	Left
	MMRII	1	2 (Day 0)	SC	Deltoid	Left
	Varivax	1	2 (Day 0)	SC	Deltoid	Right
MMR+V→HAV	MMRII	1	2 (Day 0)	SC	Deltoid	Left
	Varivax	1	2 (Day 0)	SC	Deltoid	Right
	Havrix	1 2	3 (Day 42) 4 (Month 7.5-10.5)	IM	Thigh	Left

IM=intramuscular, SC=subcutaneous; Thigh (anterolateral); deltoid (outer region)
Source: STN 103475/5343, Module 5.3.5.1, CSR HAV-231, Table 5, p. 47

The first 1080 subjects were to be randomized 1:1:1. Following amendment 4 to the protocol, 388 additional subjects were planned for enrolment into the concomitant group (HAV+MMRII+V) or the sequential group (MMRII+V→HAV) utilizing a 1:1 randomization scheme. A total of 1474 subjects were enrolled at 50 study sites by 36 investigators in the U.S., and 1241 subjects were vaccinated and included in the Total Vaccinated Cohort (TVC).

The gender distribution of subjects in the clinical trial was 47.1% female and 52.9% male.

The race distribution of subjects in the clinical trial was 68.7% White; 16.4% Hispanic (Black and White); 8.5% Black; 1.2% Asian; 0.4% North African; and 5.0% other.

Immunogenicity in Study HAV-231

Table 2 presents the pre-specified primary endpoints for all five antigens (hepatitis A, measles, mumps, rubella and varicella) and post-hoc primary endpoints for seroresponse to measles, mumps and varicella vaccinations as recommended by the CMC reviewers.

Table 2: Havrix, MMRII and Varivax Primary Endpoints and Non-Inferiority Criteria

Vaccine Component	Primary Endpoint Pre-specified	Primary Endpoint Post-Hoc	Non-Inferiority Criteria
Hepatitis A ATP seronegative (<15 mIU/mL)	GMCs ≥15 mIU/mL and % of subjects with GMCs ≥15 mIU/mL @ 30 days after dose 2 HAV	NA	LB of the 95% CI for the difference SP rates (HAV+MMRII+V minus HAV alone) is >-5% AND LB of the 95% CI for the GMC ratio (HAV+MMRII+V÷HAV) is >0.5
Rubella ATP seronegative (<4 IU/mL)	Antibody titer >10 @ 42 days after receipt MMRII+V	NA	LB of the 95% CI for the difference in SR rates (HAV+MMRII+V minus MMRII+V→HAV) is >-5%
Measles ATP seronegative (<150 mIU/mL)	Antibody ≥150 mIU/mL @ 42 days after receipt MMRII+V	Antibody > 200 mIU/mL @ 42 days after receipt MMR+V	LB of the 95% CI for the difference in SC rates (HAV+MMRII+V minus MMRII+V→HAV) is >-5%
Mumps ATP seronegative (titer < 28)	Antibody titer ≥28 @ 42 days after receipt MMRII+V	Antibody titer <24 prior to and ≥51 @ 42 days after receipt of MMRII+V	LB of the 95% CI for the difference in SC rates (HAV+MMRII+V minus MMRII+V→HAV) is >-5%
Varicella ATP seronegative (titer < 5)	Antibody titer ≥5 @ 42 days after receipt of MMRII+V	Antibody titer <40 prior to with ≥4-fold rise in titer @ 42 days after receipt of MMRII+V	LB of the 95% CI for the difference in SC rates (HAV+MMRII+V minus MMRII+V→HAV) is >-10%.

ATP=According to Protocol; GMC=Geometric Mean Concentration
SP=seropositivity; SR=seroresponse; SC=seroconversion

For each of the five antigens in the three vaccines studied, the immune response to hepatitis A after concomitant administration of Havrix with MMRII and Varivax was non-inferior to Havrix alone, and the immune responses to measles, mumps, rubella and varicella were non-inferior when all three vaccines were administered concomitantly as compared to when MMRII and Varivax were administered separately from Havrix as defined by pre-specified statistical criteria displayed in Table 2. These criteria were met in the According To Protocol cohort (ATP) and Total Vaccinated Cohort (TVC) (see

Table 3 [anti-HAV seropositvity], Table 4 [anti-HAV GMCs], and Table 5 [anti-measles, mumps and varicella seropositivity; anti-rubella seroresponse]). These are presented in Table 3 and Table 4 below (hepatitis A) and Table 5 (measles, mumps, rubella and varicella).

Table 3: Study HAV-231 – Difference in anti-HAV seropositivity ratesbetween HAV+MMR+V group and HAV group in terms of anti-HAV seropositivity rates, 31 days after dose 2 of Havrix (ATP and *TVC* cohorts for immunogenicity) [pre-specified]

				Difference in seropositivity rate (HAV+MMR+V minus HAV group)		
Group	N (%)	Group	N (%)	Difference	%	95% CI
HAV	206 (99.0%)	HAV+MMR+V	215 (99.5%)	HAV+MMR+V – HAV	0.51% [ATP]	-1.71, 3.06
HAV	*259 (98.1%)*	*HAV+MMR+V*	*268 (99.3%)*	*HAV+MMR+V – HAV*	*1.18% [TVC]*	*-0.98, 3.98*

N = number of subjects with available results
% = percentage of subjects with anti-HAV concentration ≥15 mIU/mL
95% CI = 95% Standardized asymptotic confidence interval
Note: Subjects in the HAV+MMR+V Group who were enrolled after protocol amendment 4 were not included.
Source: STN 103475/5343, CSR HAV-231, Module 5.3.5.1, Table 19, p. 79 and Supplement 26, p. 151

Table 4: Study HAV-231 – Adjusted ratios of anti-HAV GMCs between the HAV+MMR+V group and the HAV group, 31 days after dose 2 Havrix (ATP and *TVC* cohorts for immunogenicity) [pre-specified]

HAV+MMR+V group		HAV group		Adjusted GMC ratio (HAV+MMR+V group/HAV group)	
N	Adjusted GMC	N	Adjusted GMC	Value	95% CI
196	1932.8	194	1374.1	1.41 [ATP]	1.14, 1.74
247	*1861.4*	*245*	*1301.0*	*1.43 [TVC]*	*1.18, 1.74*

N = number of subjects with available results
Adjusted GMC = geometric mean antibody concentration adjusted for baseline concentration
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Note: Subjects in the HAV+MMR+V Group who were enrolled after Protocol amendment 4 were not included.
Source: STN 103475/5343, CSR HAV-231, Module 5.3.5.1, Table 20, p. 80 and Supplement 27, p. 151

Table 5: Anti-measles, anti-mumps, anti-varicella seroconversion and anti-rubella seroresponse in the MMR+V→HAV group, 42 days following the dose of MMRII and Varivax (ATP and *TVC* cohorts for immunogenicity) [pre-specified]

	MMR+V→HAV group	HAV+MMR+V group	Difference in seropositivity/seroconversion rates (HAV+MMR+V minus MMR+V→HAV group)	
Antibody	N (%)	N (%)	% difference	95% CI
Anti-measles	250 (98.8%)	268 (99.6%)	0.83%	-1.00, 3.14%
Anti-measles	*357 (99.2%)*	*346 (99.1%)*	*-0.03%*	*-1.77, 1.68%*
Anti-mumps	197 (98.0%)	212 (97.6%)	-0.33%	-3.64, 3.03%
Anti-mumps	*269 (97.8%)*	*273 (97.8%)*	*-0.02%*	*-2.80, 2.76%*
Anti-rubella	247 (99.6%)	271 (99.6%)	0.04%	-1.69, 1.92
Anti-rubella	*355 (99.4%)*	*349 (99.4%)*	*0.01%*	*-1.56, 1.52*
Anti-varicella	171 (98.2%)	193 (96.9%)	-1.35%	-5.11, 2.08
Anti-varicella	*240 (98.8%)*	*238 (96.6%)*	*-2.11%*	*-5.40, 0.68*

Anti-measles seroconversion defined as: Seronegative (<150 mIU/mL) subjects at pre-vaccination having antibody titers ≥ 150 mIU/mL at post vaccination; Anti-mumps seroconversion defined as: Subjects with titers < 28 at pre-vaccination having antibody titer ≥ 28 post-vaccination; Anti-rubella seroresponse defined as: Seronegative (<4 IU/mL) subjects at pre-vaccination having titers ≥10 IU/mLat post-vaccination; Anti-varicella seroconversion defined as: Seronegative subjects (< 5) at pre-vaccination having antibody titers ≥5 post -vaccination
N = number of subjects with with pre- and post-vaccination results available; 95% CI = 95% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit;
Source: STN 103475/5343, Module 5.3.5.1, CSR HAV-231, Table 26, p. 84

Post-hoc analyses were requested for the immune responses to measles, mumps and varicella vaccines (Table 2). These analyses were requested in light of revisions of the CBER definition of seroconversion for measles, mumps and varicella that occurred subsequent to the completion of Study HAV-231. Using the more clinically relevant definitions of seroconversions as advised in the separate INDs, non-inferiority was demonstrated for immune response to measles vaccine in the ATP and TVC cohorts (using the 95% CI around difference in seroconversion rates as >-5%), and non-inferiority in immune responses to varicella was also demonstrated in the ATP cohort (LB of the 95% CI around the difference in seroconversion rates was >-10%).

When using the revised definition for immune response to mumps vaccine, the LB of the 95% CI around difference in seroconversion rates between the concomitant vaccine group and the non-concomitant vaccine groups was -7.23%, which fell outside of the pre-specified LB for non-inferiority of -5.0%. Several factors were considered in evaluating the clinical relevance of this finding. As noted above, the pre-specified immunogenicity criteria were met for all five antigens. The study had been completed prior to communication to GSK of immunogenicity targets for measles, mumps and varicella vaccinations. Accordingly, this study was not powered to demonstrate a statistically significant difference in immune response to mumps vaccine when administered concomitantly with Varivax and Havrix as compared to when administered with Varivax alone. Additionally, the seroconversion rates for mumps were very similar for the concomitant and non-concomitant groups and the numerical difference in seropositivity rates using the revised definition for seroconversion was small (1.9% in the ATP cohort and 2.73% in the TVC cohort). The CMC assay reviewer for mumps immune response noted that rates of seroconversion using the assay selected for this study were lower as compared to historical rates of seroconversion to mumps vaccine cited in earlier studies. Given the above reasons, and because it appears unlikely that Havrix interferes with

immune response to mumps antigen as compared to when MMRII and Varivax are administered without Havrix, this clinical reviewer concludes that Havrix may be coadministered with MMRII + Varivax without clinically relevant interference in immune responses to the five antigens.

The results of the updated immune responses for measles, varicella and mumps are shown in Tables 6, 7, and 8.

Table 6: Study HAV-231- Difference between the HAV+MMR+V Group and the MMR+V→HAV Group in terms of anti-measles seroconversion 42 days following the dose of MMRII and Varivax (ATP and *TVC* cohorts for immunogenicity) [post-hoc analysis using revised definition for measles seroconversion]

	MMR+V→HAV group	HAV+MMR+V group	Difference in measles seroconversion rates (HAV+MMR+V minus MMR+V→HAV group)	
Antibody	n/N (%)	n/N (%)	% difference	95% CI
Anti-measles (ATP)	247/250 (98.8%)	267/268 (99.6%)	0.83%	-1.00, 3.14%
Anti-measles (TVC)	*354/357 (99.2%)*	*343/346 (99.1%)*	*-0.03%*	*-1.77, 1.68*

Seronegative = anti-measles antibody concentration < 150 mIU/mL prior to vaccination.
Seroconversion: For initially seronegative subjects, anti-measles antibody concentration ≥ 200mIU/mL at Day 42 post-vaccination
N=number of subjects with both pre-and post-vaccination results available
N=number of seroconverted subjects; %=percentage of seroconverted subjects
Source: STN 103475/5343.5001, Module 1.11.3, Response to 06Dec2010 FDA comments, submitted 12/22/10, able 2, p. 2 and Table 4, p. 3

Table 7: Study HAV-231- Difference in anti-varicella seroconversion between the HAV+MMR+V Group and the MMR+V→HAV Group 42 days following the dose Varivax using cut-off 40 1/DIL and 4-fold increase in originally seronegative subjects (ATP and *TVC* cohorts for immunogenicity) [post-hoc analysis using revised definition for varicella seroconversion]

	MMR+V→HAV group	HAV+MMR+V group	Difference in seropositivity/seroconversion rates (HAV+MMR+V minus MMR+V→HAV group)	
Antibody	N (%)	N (%)	% difference	95% CI
Anti-varicella (ATP) – post-hoc	173/180 (96.1%)	192/201 (95.5%)	-0.59%	-4.93, 3.87%
Anti-varicella (ATP) –pre-specified	168/171 (98.2%)	187/193 (96.9%)	-1.35%	-5.11, 2.08%
Anti-varicella (TVC) – post-hoc	243/252 (96.4%)	237/250 (94.8%)	-1.6%	*
Anti-varicella (TVC) pre-specified	*240 (98.8%)*	*238 (96.6%)*	*-2.11%*	*-5.40, 0.68%*

Seronegative = antibody titers to varicella < 40 1/DIL prior to vaccination.
Seroconversion: For initially seronegative subjects, a 4-fold rise in antibody titer at P1 (D42 post-vaccination) pre-specified analyses using cut-off 5 1/DIL]
N=number of subjects with both pre- and post-vaccination results available
n= number of seroconverted subjects; %=percentage of seroconverted subjects
*: 95% CI around the difference were not provided for the TVC (but 95% CIs around the percentages do overlap)
Source: STN 103475.5343.0, 103475/5343.5001, Module 1.11.3, Response to 06Dec2010 FDA comments, submitted 12/22/10, Table 10, p. 7; and STN 103475/5343.5002, Module 1.11.3, Response to 06DEC2010 and 13JAN2011, submitted 2/1/11, Table 1, p. 1

Table 8: Study HAV-231- Difference in anti-mumps seroconversion between the HAV+MMR+V Group and the MMR+V→HAV Group 42 days following the dose of MMRII and Varivax (ATP and *TVC* cohorts for immunogenicity) [post-hoc analysis with revised definition for mumps seroconversion and compared to pre-specified definition]

	MMR+V→HAV group	HAV+MMR+V group	Difference in mumps seroconversion rates (HAV+MMR+V minus MMR+V→HAV group)	
Antibody	n/N (%)	n/N (%)	% difference	95% CI
Anti-mumps (ATP)-post-hoc definition	190/207 (93.7%) [95% CI: 89.2, 96.7%]	178/190 (91.8%) [95% CI: 87.2, 95.1%]	-1.90%	-7.23, 3.43%
Anti-mumps (ATP)-pre-specified definition	193/197 (98.0%)	207/212 (97.6%)	-0.33%	-3.64, 3.03%
Anti-mumps (TVC)-post-hoc definition	*249/267 (93.3%)*	*239/264 (90.5%)*	*-2.73%*	*-7.58, 1.98%*
Anti-mumps (TVC)-pre-specified definition	*269/275 (97.8%)*	*273/279 (97.8%)*	*-0.02%*	*-2.80, 2.76%*

Seronegative=anti-mumps antibody concentrations < 24 prior to vaccination.
Seroconversion: For initially seronegative subjects, anti-mumps antibody concentration ≥ 51 at Day 42 post-vaccination.
N=number of subjects with both pre-and post-vaccination results available
n=number of seroconverted subjects; %=percentage of seroconverted subjects
pre-specified analyses from <28 to ≥28 at 42 days post-vaccination
Source: STN 103475/5343.5001, Module 1.11.3, Response to 06Dec2010 FDA comments, submitted 12/22/10, Table 6, p. 5 and Table 8, p. 6

Additional post-hoc analyses were conducted for all antigens when excluding subjects from one center where one investigator received more than a specified amount of financial remuneration from GSK, although the financial remuneration was not related to the present study. Conclusions reached were not altered when excluding subjects from this one center.

Safety in Study HAV-231

Incidence of any symptom (solicited and unsolicited) in the four days after vaccination overall per subject

Symptoms in the fours days after vaccination are presented in Table 9.

Table 9: Study HAV-231 – Incidence of any symptom (solicited and unsolicited) symptoms in the 4 days after vaccination after Doses 1 and 2 Havrix, after MMR+V, and overall/subject (by treatment group) (Total Vaccinated Cohort)

Group	Any symptom	General symptom	Local symptom
	n/N (%)	n/N (%)	n/N (%)
HAV	259/324 (79.9%)	228/324 (70.4%)	142/324 (43.8%)
HAV+MMR+V	384/462 (83.1%)	347/462 (75.1%)	236/462 (51.1%)
MMR+V→HAV	386/455 (84.8%)	360/455 (79.1%)	231/455 (50.8%)
	Any Grade 3 symptom	Any Grade 3 General symptom	Any Grade 3 Local symptom
HAV	18/324 (5.6%)	15/324 (4.6%)	3/324 (0.9%)
HAV+MMR+V	33/462 (7.1%)	25/462 (5.4%)	10/462 (2.2%)
MMR+V→HAV	44/455 (9.7%)	36/455 (7.9%)	13/455 (2.9%)

N=number of subjects with at least one administered dose.
n=number of subjects presenting at least one type of symptom whatever the study vaccine administered; %=percentage of subjects presenting at least one symptom whatever the study vaccine administered
Source: STN 103475/5343, Module 5.3.5.1, CSR 231, Table 27, p. 87

While reports of symptoms generally were balanced between the three groups, individuals receiving MMR+V, followed at 42 days by HAV more frequently reported Grade 3 symptoms than did the groups receiving HAV alone and concomitant administration of HAV with MMRII and Varivax. The reasons for this finding were investigated. The 95% CIs around Grade 3 symptoms overall/subject were overlapping. The subjects in the sequential dosing had three separate vaccination visits as compared to two vaccination visits for the other two groups, and there was little difference in occurrence of any Grade 3 symptoms when considered overall/dose (3.1% in the HAV group, 3.8% in the MMR+V+HAV group, and 4.0% in the MMR+V→HAV group). GSK conducted an exploratory analysis using the standardized asymptotic 95% CIs and the associated 2-sided p-values to detect group difference for these solicited local and general symptoms. In these exploratory analyses, the sequential group experienced higher incidences of ≥ grade 2 irritability and ≥ grade 2 loss of appetite when considered overall/subject. GSK cautioned that such exploratory analyses were to be considered with caution since there was no adjustment for multiplicity of endpoints and that a difference deemed significant statistically might not have clinical significance. The occurrence of these events did not translate into higher rates of discontinuation from the study.

Solicited Injection Site Adverse Reactions in the four days after vaccination (overall, after dose 1 Havrix and after dose 2 Havrix)

Solicited local reactions included pain, rash, redness and swelling. Although there were higher proportions of subjects in the concomitant group with pain, redness and swelling in the concomitant administration group (HAV+MMRII+V) as compared to Havrix alone (HAV), the proportions of subjects with Grade 3 solicited local symptoms were similar in all groups (Table 10).

Table 10: Study HAV-231 - Incidence of solicited local reactions reported during the 4-day (Days 0–3) overall/subject(Total Vaccinated cohort)

		Pain	Rash (local)	Redness (mm)	Swelling (mm)
	N	n/%	n/%	n/%	n/%
HAV	304	103/33.9%	0/0.0%	97/31.9%	45/14.8%
HAV+MMR+V	419	187/44.6%	4/1.0%	151/36.0%	82/19.6%
MMR+V→HAV	411	162/39.4%	3/0.7%	149/36.3%	70/17.0%
		Grade 3 pain	Grade 3 rash	Grade 3 redness (>20 mm)	Grade 3 swelling (>20 mm)
	N	n/%	n/%	n/%	n/%
HAV	304	0/0.0%	0/0.0%	1/0.3%	3/1.0%
HAV+MMR+V	419	4/1.0%	0/0.0%	2/0.5%	4/1.0%
MMR+V→HAV	411	7/1.7%	0/0.0%	5/1.2%	2/0.5%

N=number of subjects with at least one administered dose.
n=number of subjects presenting at least once the symptom; %=percentage of subjects presenting at least once the symptom
Source: STN 103475/5343, Module 5.3.5.1, CSR 231, Table 28, p. 88

In exploratory analyses of the differences in rates overall per subject (conducted by GSK as follows: the standardized asymptotic 95% CIs and the associated 2-sided p-values to detect group difference were computed for the difference in the percentage of subjects between the vaccine groups reporting specified solicited local and general symptoms in the 4 day post-vaccination period), the rate of pain and rash at the injection site was

significantly higher in the concomitant group as compared to the Havrix alone group (p=0.0125 for pain and p=0.0445 for rash). Given the similarity in Grade 3 rates of pain in both groups, however, these differences were unlikely to be clinically meaningful.

In review of solicited local adverse reactions in the four days after dose 1 and dose 2 of Havrix in the Havrix alone group and the concomitant administration group, the proportions of subjects with such reactions were generally similar. These are presented in Table 11.

Table 11: Study HAV-231 – Solicited Local Adverse Reactions Occurring Within 4 Days of Vaccination with Havrix alone or Havrix administered Concomitantly With MMRII and Varivax (TVC)

	Dose 1 Havrix		Dose 2 Havrix	
	Havrix alone	**Havrix + MMRII+V**	**Havrix alone**	**Havrix + MMRII+V**
N	298	411	272	373
Pain, any	23.8%	23.6%	24.3%	30.3%
Redness, any	20.1%	23.6%	22.8%	23.9%
Swelling, Any	8.7%	10.2%	9.6%	9.9%

N=number of subjects with at least one administered dose.
%=percentage of subjects presenting at least once the symptom
Source: STN 103475/5343, Module 5.3.5.1, CSR 231, Supplement 34, p. 156-159

Systemic Adverse Experiences in the four days after vaccination

Overall, the subjects in the concomitant group (HAV+MMRII+V) experienced a higher rate of drowsiness as compared to the Havrix group alone, but rates of Grade 3 drowsiness were similar in the three treatment groups. Overall, the rates of all other solicited general symptoms in the Havrix alone and HAV+MMRII and V groups were otherwise similar (Table 12).

Table 12: Study HAV-231 - Incidence of solicited general symptoms reported during the 4-day (Days 0–3) post-vaccination period according and overall-per-subject analysis (Total Vaccinated cohort)

Symptom	Grade	HAV group N=304	HAV+MMR+V N=424	MMR+V→HAV N=411
		n/%	n	n
Drowsiness	Any Grade 3	95/31.3% 6/2.0%	178/42.0% 9/2.1%	179/43.6% 8/1.9%
Fever (Axillary)	≥37.5°C >38.0°C >38.5°C >39.0°C	54/17.8% 18/5.9% 11/3.6% 3/1.0%	80/18.9% 29/6.8% 16/3.8% 7/1.7%	110/26.8% 40/9.7% 19/4.6% 12/2.9%
Irritability	Any Grade 3	144/47.4% 5/1.6%	216/50.9% 9/2.1%	238/57.9% 9/2.2%
Loss of Appetite	Any Grade 3	94/30.9% 4/1.3%	154/36.3% 7/1.7%	170/41.4% 9/2.2%
Rash	Any Grade 3	5/1.6% 0/0.0%	10/2.4% 0/0.0%	7/1.7% 0/0.0%

N= number of subjects with at least one documented dose; n= number of subjects reporting at least once the symptom; %=percentage of subjects reporting at least once the symptom
Source: STN 103475/5343, Module 5.3.5.1, CSR HAV-231, Table 32, p. 95-96

In the exploratory analysis conducted by GSK (method noted above), the difference in rate of drowsiness was statistically higher in the concomitant group as compared to the Havrix alone group (p=0.0067). Given the similarity in Grade 3 rates of drowsiness, however, this finding was not considered clinically important.

In review of solicited general adverse events in the four days after dose 1 and dose 2 of Havrix in the Havrix alone group and the concomitant administration group, a higher proportion of subjects with any drowsiness, irritability and loss of appetite were reported in the comcomitant group as compared to the Havrix alone group. Grade 3 solicited general adverse events were reported in ≤ 1.5% after any dose Havrix when administered alone and ≤ 2.2% after any dose Havrix when administered concomitantly with MMR and Varivax, and did not contribute to premature discontinuations from the study. These results are presented in Table 13.

Table 13: Study HAV-231 – Solicited Local Adverse Reactions Occurring Within 4 Days of Vaccination with Havrix alone or Havrix administered Concomitantly With MMRII and Varivax (TVC)

	Dose 1 Havrix		Dose 2 Havrix	
	Havrix alone	**Havrix + MMRII+V**	**Havrix alone**	**Havrix + MMRII+V**
N	300	417	271	375
Irritability, any	33.3%	43.9%	31.0%	27.2%
Irritability, grade 3	0.3%	1.9%	1.5%	0.3%
Drowsiness, any	22.3%	35.3%	21.0%	20.8%
Drowsiness, grade 3	1.0%	2.2%	1.1%	0.0%
Loss of appetite, any	18.3%	26.1%	19.9%	20.5%
Loss of appetite, grade 3	1.0%	1.4%	0.4%	0.3%
Fever ≥100.6°F (38.1°C)	3.0%	4.8%	3.3%	2.7%
Fever ≥101.5°F (38.6°C)	2.0%	2.6%	1.8%	1.6%
Fever ≥102.4°F (39.1°C)	0.7%	0.7%	0.4%	1.1%

N=number of subjects with at least one administered dose.
%=percentage of subjects presenting at least once the symptom
Source: STN 103475/5343, Module 5.3.5.1, CSR 231, Supplement 35, p. 160-161

Serious Clinical Adverse Experiences

Thirty-three subjects experienced a serious adverse event during the study: seven (2.2%) subjects were in the HAV group, sixteen (3.5%) subjects were in the HAV+MMRII+V group, and ten (2.2%) subjects were in the MMRII+V→HAV group. Thirty-two of 33 of these serious adverse events were assessed by the clinical investigator as unrelated to receipt of study vaccines. In the concomitant group, one subject was diagnosed as having autism at 89 days after receipt of Havrix, MMRII and Varivax. The clinical investigator could not definitively exclude receipt of vaccines as related to this event because the event occurred three months after dose 1 of the concomitant vaccines. In this study, two other subjects were diagnosed with autism, one at 91 days after receipt of Havrix alone and one subject in the concomitant group on the day of dose 2 of Havrix (approximately 42 days after dose 1 of all three vaccines together). In light of a review of the family history of one of these subjects, a history of developmental problems prior to the receipt of any study vaccines existing in another subject diagnosed with autism and concomitant medical issues in these subjects, along with review of large epidemiological studies conducted in Denmark and Japan in several hundred thousand children and recent review

in the British Medical Journal regarding vaccines and autism, the totality of the evidence does not support a relationship between receipt of MMR vaccines and/or Havrix and the development of autism. One child who received Havrix alone was diagnosed as having acute lymphoblastic leukemia at 222 days after receipt of dose 1. This event was assessed as unrelated to study vaccines, and the subject was withdrawn from the study.

Deaths
One sudden death was reported at 6 months after receipt of Havrix, MMRII and Varivax (child found in the crib with evidence of anoxic brain injury on subsequent autopsy after resuscitation efforts and short stay in pediatric ICU). This death was assessed by the clinical investigator as unrelated to receipt of vaccines. The lengthy time interval between vaccination and event make a relationship to study vaccines highly unlikely.

COMBINED SAFETY IN STUDIES HAV-210, HAV-220, HAV-232 AND HAV-232
Safety Database Children 11-25 months of age: Overall, 3,152 children received Havrix with or without other commonly administered childhood vaccines in study HAV-210 (Infanrix and Hib conjugate vaccine), HAV-220 (pneumococcal 7-valent conjugate vaccine), HAV-232 (Infanrix and Hib conjugate vaccine), and HAV-231 (measles, mumps, rubella and varicella vaccines). Of the 3,152 children, 1,332 received Havrix alone, 909 children received Havrix concomitantly with other childhood vaccines, and 911 children received Havrix following the other routine childhood vaccines. Safety follow-up and reporting were similar for all four studies.

Demographics: The mean age of participants in the four studies was 15.0 months overall. 48.2% of subjects were female and 51.8% were male. The ethnic breakdown was as follows: 10.2% black, 64.3% white/Caucasian, 17.1% American Hispanic, and 8.4% other.

Safety in Combined Studies
Solicited Injection Site Adverse Reactions in the four days after vaccination in all studies
Solicited local adverse reactions at the Havrix administration site included pain, redness and swelling. As noted in study HAV-231, the largest of the four studies, overall/subject, pain was the most frequently reported solicited local adverse reaction in [23.8%, 23.6%] after dose 1 and [24.3%, 30.3%] after dose 2 Havrix [Havrix alone, concomitantly with MMR+ Varivax, respectively]. Redness was reported in [20.1%, 20.0%] after dose 1 and [22.8%, 23.9%] after dose 2 Havrix [Havrix administered alone, concomitantly with MMR+Varivax, respectively]. Swelling was reported in [8.7%, 10.2%] after dose 1 Havrix and [9.6%, 9.9%] after dose 2 Havrix [Havrix administered alone, concomitantly with MMR+Varivax, respectively]. Grade 3 solicited local adverse events (pain, redness and swelling) were reported in $\leq$1.0% of subjects after any dose Havrix within this study.

The proportions of subjects with solicited local reactions at the Havrix injection site were similar in the three other coadministration studies, i.e., HAV-210, HAV-220 and HAV-232, in that local reactogenicity at the Havrix injection site was generally similar whether Havrix was administered alone or concomitantly with other childhood vaccines.

Systemic Adverse Experiences in the four days after vaccination in all studies
Solicited systemic adverse events included drowsiness, irritability, loss of appetite, and fever ≥37.5°C. As noted in study HAV-231, which was the largest study in the four concomitant administration studies for subjects 11-25 months of age, the following proportions of subjects reported these symptoms after dose 1 and dose 2, respectively: irritability 33.3% and 31.0%; drowsiness 22.3% and 21.0%; loss of appetite 18.3% and 19.9%; and fever 12.0% and 8.1%. When Havrix was administered concomitantly with MMR and Varivax at dose 1, the following proportions of subjects reported these symptoms after dose 1 and dose 2, respectively: 43.9% and 27.2%; drowsiness 35.3% and 20.8%; loss of appetite 26.1% and 20.5%; and fever 14.6% and 7.5%. Grade 3 solicited general adverse events were reported in ≤ 1.5% after any dose Havrix when administered alone and ≤ 2.2% after any dose Havrix when administered concomitantly with MMR and Varivax, and did not contribute to premature discontinuations from the study. Similar patterns were observed in the other studies in which Havrix was administered with pneumococcal 7-valent conjugate vaccine (study HAV-220) or Infanrix and Hib conjugate vaccine (study HAV-232).

Unsolicited Adverse Events in the 31 days after vaccination in all studies
In the 31 days after any vaccination in the Havrix alone group, 58.3% of subjects reported such events. Upper respiratory infections (14.3%), otitis media (11.7%) and pyrexia (8.3%) were the most frequently reported unsolicited adverse events across studies. Other frequently reported unsolicited adverse events in the Havrix alone group (>5%) included diarrhea (7.0%), cough (5.8%), and vomiting (5.4%). Grade 3 unsolicited adverse events occurred in 5.8% of these subjects.

In the 31 days after vaccination with Havrix and other childhood vaccines concomitantly or sequentially, 57.5% of subjects experienced an unsolicited adverse event in the 31 days after vaccination. The events and proportion were generally similar in these treatment groups, with upper respiratory infections in 14.8%, otitis media in 14.3%, and fever/pyrexia in 10.0% of subjects. Other frequently reported (>5%) unsolicited adverse events in these treatment groups included rhinitis/rhinorrhea (6.1%), diarrhea (6.0%), and cough (5.2%). Grade 3 unsolicited adverse events occurred in 7.3% of subjects in the concomitant/sequential groups overall.

Serious Clinical Adverse Experiences throughout all studies
Within the 30 day period following any dose of Havrix in four studies, 29/3152 (0.9%) of all subjects experienced a serious adverse event after any dose Havrix, whether administered alone, concomitantly with other vaccines, or 30-42 days following the other specified childhood vaccines. Among subjects administered Havrix alone, 21/2243 (0.9%) experienced a serious adverse event within 30 days after receipt of any dose Havrix. Among subjects who received Havrix concomitantly with one or more of the other specified childhood vaccine(s), 8/909 (0.9%) experienced a serious adverse event in this time period. There were four reports of seizures within 30 days of receipt of any dose of Havrix (three occurred 2, 9, and 27 days after dose 1 Havrix and one occurred 12 days after dose 2 Havrix). Bronchial hyperreactivity/respiratory distress was reported in one

subject on the day of receipt of dose 1 Havrix alone. The majority of these events were assessed as unrelated to study vaccines and were generally associated with other concurrent conditions.

Deaths in all studies
Two deaths were reported in the four studies. One was as described in study HAV-231 above. The second death involved a 31 month old male which was caused by accidental strangulation with Venetian blind cord at 31 days after dose 2 Havrix.

6. Statistical Review

Both the co-primary immunogenicity objectives of study HAV-231 were met. Specifically, non-inferiority (NI) between the concomitant and non-concomitant HAV vaccination groups was demonstrated for anti-HAV seropositivity rates (NI margin = 10% and GMCs (NI margin defined as a 2-fold difference in anti-HAV GMC when Havrix was administered alone compared to when Havrix was co-administered with MMRII and Varivax). The seropositivity rates and corresponding GMCs at 31 days after the second dose of Havrix were 99.0% (GMV=1933) and 99.5% (GMC=1374) for the HAV group and the HAV+MMRII+V group, respectively.

Non-inferiority also was demonstrated for anti-measles (NI margin = 5%), anti-mumps (NI margin = 5%), and anti-varicella (NI margin = 10%) seroconversion rates and anti-rubella (NI margin = 5%) seroresponse rates between the HAV+MMRII+V and MMRII+V→HAV groups. At 42 days following vaccination with MMRII and Varivax, the seroconversion rates (HAV+MMRII+V vs. MMRII+V→HAV) were 99.6% vs. 98.8% for anti-measles, 97.6% vs. 98.0% for anti-mumps, and 96.9% vs. 98.2% for anti-varicella antibodies, respectively. The seroresponse rates for anti-rubella antibodies were 99.6% for both groups.

When using revised seroconversion definitions for anti-measles, anti-varicella, and anti-mumps, the non-inferiority objectives were met for the anti-measles response and the anti-varicella response, but was not met for the anti-mumps response. The lower limit of the two-sided 95% CI of the difference in anti-mumps seroconversion rate (HAV+MMRII+V minus MMRII+V →HAV) was -7.23%, below the non-inferiority margin of -5%, a finding that was not considered clinically important (see clinical discussion).

7. Clinical Pharmacology

See section 5 of this SBRA.

8. Advisory Committee Meeting

There were no product-specific concerns that would have benefited from an advisory committee discussion.

9. Other Relevant Regulatory Issues

Pediatrics

Safety and immunogenicity data from study HAV-231included in this supplement satisfactorily fulfill STN 103475/5190 post-marketing commitment #3 (approval letter dated 10/17/05). Further, combined safety data from studies HAV-210, HAV-220, HAV-232 and HAV-231 satisfactorily fulfill STN 103475/5190 post-marketing commitment #1 (approval letter 10/17/05) and Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) requirements. Since post-marketing commitment #2 was fulfilled by study HAV-220 (STN 103475/5195), and post-marketing commitment #4 was fulfilled by study HAV-232 (STN 103475.5284), all four post-marketing commitments have been fulfilled, and no further concomitant administration pediatric studies will be required by the Agency at this time.

10. Bioresearch monitoring (BiMO) inspections

No issues were identified during BiMO inspections which would impact on approval of this supplement.

11. Labeling

The package insert was revised to include safety and immunogenicity data for study HAV-231, as well as overall safety for studies HAV-210, HAV-220, HAV-232, and HAV-231 combined. Concomitant administration of MMRII and Varivax was added to section 7 (Drug Interactions), and updates were included in section 6 (Adverse Events), and section 14 (Clinical Studies section).

12. Recommendations

The review committee recommends approval of the BLA supplement to include immunogenicity and safety data to support concomitant administration of Havrix with MMRII and Varivax among children 12-15 months of age, and to include overall safety data in approximately 3000 children who received Havrix, administered alone or concomitantly with other childhood vaccines in the second year of life [including pneumococcal 7-valent conjugate vaccine (Prevnar); Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (Infanrix); Haemophilus b conjugate vaccine (ActHIB); measles, mumps and rubella vaccine (MMRII); and varicella vaccine (Varivax)].