

Summary Basis of Regulatory Action (SBRA)

Date: September 9, 2016

From: Carmen M. Collazo-Custodio, Ph.D., Chair of the Review Committee

BLA/STN: 125419/39

Applicant Name: ID Biomedical Corporation of Québec [doing business as (dba) GlaxoSmithKline Biologicals] – (the Applicant is referred to as GSK in this document)

Date of Submission: November 10, 2015

CBER Received Date: November 12, 2015

PDUFA Goal Date: September 9, 2016 (*September 11, 2016, is Sunday*)

Proprietary Name: None

Proper Name: Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (this vaccine is also referred to as the Q-Pan H5N1 vaccine in this document)

Indication: Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is a vaccine indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is approved for use in persons 6 months and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

Recommended Action: Approval

Signatory Authorities Action: Approval

Office Signatory Authority: Wellington Sun, M.D., Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research

- 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.**

Specific documentation used in developing the SBRA	Reviewer Name– Document(s) Date
Clinical Review	Darcie Everett, M.D., M.P.H. – September 9, 2016
Pharmacovigilance Review	Maria Said, M.D., M.P.H. – September 8, 2016
Statistical Review, Clinical	Rong Fu, Ph.D. – August 11, 2016; August 17, 2016, Addendum
Statistical Review, Bioassay	Rong Fu, Ph.D. – August 3, 2016
Bioresearch Monitoring Review	Haecin Chun – July 5, 2016
Product Review, Bioassay	Hana Golding, Ph.D. – June 21, 2016
Labeling Review	Sonny Saini, Pharm.D., MBA – August 4, 2016 Ramachandra Naik, Ph.D. – September 9, 2016

1. Introduction

Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (hereafter referred to as the Q-Pan H5N1 vaccine) was approved on November 22, 2013, for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. Q-Pan H5N1 was approved for use in persons 18 years of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine. On November 12, 2015, CBER received a Biologics License Application (BLA) supplement from GSK (U.S. license 1739), designated STN 125419/39, to extend the age range for use to include persons 6 months through 17 years of age. Thus, with the approval of this supplement, Q-Pan H5N1 will be licensed for use in persons 6 months of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

This pediatric supplement includes data from a clinical study, Q-PAN H5N1=AS03-021 (Protocol 114464), which was a phase 2/3, randomized, controlled, observer-blind, multi-center trial to evaluate the safety and immunogenicity of a two-dose primary vaccination series of the Q-Pan H5N1 vaccine in children 6 months to < 18 years of age (conducted under BB-IND 13413). Moreover, GSK included in this supplement data from a non-IND clinical study, FLU Q-Pan H1N1-035. This was a phase 3, observer-blind, randomized, controlled, multi-center, multi-country trial that assessed the safety and relative efficacy of a related monovalent AS03-adjuvanted pandemic influenza virus vaccine (Q-Pan H1N1) compared to the monovalent unadjuvanted vaccine in children 6 months through 9 years of age. Q-Pan H1N1 is a non-U.S. licensed vaccine manufactured in Québec, Canada, by the same process as for the Q-Pan H5N1 vaccine (Table 1). In support of licensure of Q-Pan H5N1 in the pediatric population, CBER reviewed the safety and immunogenicity data from study Q-PAN H5N1=AS03-021 and the safety data from study FLU Q-Pan H1N1-035.

2. Background

The Biomedical Advanced Research and Development Authority (BARDA) of the United States (U.S.) Department of Health and Human Services contracted GSK to develop and submit for licensure a candidate H5N1 influenza virus vaccine with antigen-sparing potential for inclusion in the U.S. National Stockpile. In November 2013, Q-Pan H5N1 was licensed for use in adults 18 years of age and older for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine.

The Q-Pan H5N1 vaccine consists of an inactivated, split A/H5N1 influenza virus antigen produced in eggs and an oil-in-water emulsion adjuvant (AS03 adjuvant). The H5N1 antigen component of the Q-Pan H5N1 vaccine is manufactured in Québec, Canada according to the same process as that used to produce the antigens in FluLaval and FluLaval Quadrivalent (Table 1), which are unadjuvanted seasonal influenza virus vaccines licensed in the U.S. (hence the designation Q-Pan for pandemic antigen manufactured in Québec). The AS03 adjuvant component of the Q-Pan H5N1 vaccine is manufactured and filled at GSK's facility in [REDACTED]. The AS03 adjuvant contains two biodegradable oils, squalene and α -tocopherol, mixed with an aqueous phase consisting of phosphate buffered saline. Polysorbate 80 is used as surfactant to stabilize the oil/water interface.

Table 1 provides a brief description of GSK’s egg-based influenza virus vaccines that are relevant for the discussion and understanding of the clinical development of the Q-Pan H5N1 vaccine.

Table 1. Description of GSK’s Influenza Virus Vaccines

Vaccine	Description	Haemagglutinin (HA) per 0.5 mL dose	Adjuvant
Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted	GSK’s H5N1 AS03-adjuvanted pandemic vaccine, manufactured in Québec, Canada (“Q-Pan H5N1” vaccine)	3.75 µg HA of the influenza virus strain A/Indonesia/05/2005 [^]	AS03 _A [†]
FluLaval [®]	GSK’s U.S.-licensed seasonal influenza vaccine (trivalent, inactivated, split virion), manufactured in Québec, Canada	15 µg HA of each of three influenza viruses from subtypes H1N1, H3N2 and type B	None
FluLaval [®] Quadrivalent	GSK’s U.S.-licensed seasonal influenza vaccine (inactivated, split virion), manufactured in Québec, Canada	15 µg HA of each of four influenza viruses (two A subtypes H1N1 and H3N2 and two B strains)	None
Arepanrix [™]	GSK’s H1N1 AS03-adjuvanted pandemic vaccine, manufactured in Québec, Canada (“Q-Pan H1N1” vaccine)	3.75 µg HA of A/California/7/2009 (H1N1)v-like strain (X-179A)	AS03 _A [†]
Fluarix [®]	GSK’s U.S.-licensed seasonal influenza vaccine (trivalent, inactivated, split virion), manufactured in Dresden, Germany	15 µg HA of each of three influenza viruses from subtypes H1N1, H3N2 and type B	None
Pandemrix [™]	GSK’s H1N1 AS03-adjuvanted pandemic vaccine, manufactured in Dresden, Germany by the Fluarix [®] process	3.75 µg HA of A/California/7/2009 (H1N1)v-like strain (X-179A)	AS03 _A [†]

[^] Each 0.25 mL pediatric dose contains 1.9 µg hemagglutinin (HA) of the influenza virus strain A/Indonesia/05/2005 (H5N1), and half of the amounts of the other components in the adult dose.

[†]AS03_A is “full dose” AS03 adjuvant: 10.69 mg squalene, 11.86 mg D,L-α-tocopherol and 4.86 mg polysorbate 80 per 0.5 mL dose. AS03_B is the “half dose” of AS03_A.

Note: In the SBRA document, the names of the vaccines are provided without the superscript symbol [™] or [®].

The Q-Pan H5N1 vaccine is an emulsion for intramuscular injection supplied as 2 separate vials: multi-dose vials of the H5N1 antigen suspension and the AS03 adjuvant emulsion that must be combined before use. Each 0.5 mL adult dose contains:

- 3.75 micrograms (µg) hemagglutinin (HA) of the influenza virus strain A/Indonesia/05/2005
- 5 µg thimerosal, a mercury derivative, as a preservative (< 2.5 µg mercury)
- AS03 adjuvant (10.69 mg squalene, 11.86 mg D,L-α-tocopherol, and 4.86 mg polysorbate 80)

Each 0.5 mL adult dose may also contain residual amounts of ovalbumin (≤ 0.083 µg), formaldehyde (≤ 12.5 µg), and sodium deoxycholate (≤ 3.75 µg) from the antigen manufacturing process.

Each 0.25 mL pediatric dose contains 1.9 µg HA of the influenza virus strain A/Indonesia/05/2005 (H5N1), and half of the amounts of the other components in the adult dose (listed above). The term AS03_B is used to refer to the amount of AS03 adjuvant present in the pediatric dose.

After consulting with FDA's Pediatric Review Committee (PeRC), CBER deferred submission of studies for all pediatric subgroups for the application when Q-Pan H5N1 was approved in November 2013. The reason for this deferral was because the Q-Pan H5N1 was ready for approval for use in adults and the pediatric studies had not been completed. The following deferred pediatric studies were listed in the November 22, 2013, approval letter as postmarketing requirements (PMRs) under the Pediatric Research Equity Act (PREA) [Section 505B(a) of the Federal Food, Drug, and Cosmetic Act]:

- PMR # 1: Deferred pediatric study Q-Pan H5N1=AS03-021 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy persons 6 months to < 18 years of age.
- PMR # 2: Deferred pediatric study Q-Pan-023 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy children 6 months to < 36 months of age.
- PMR # 3: Deferred pediatric study Q-Pan-024 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy persons 6 months to < 18 years of age. Study Q-Pan-024 will be conducted only if study Q-Pan-023 identifies a pediatric dose that is different than that evaluated in study Q-Pan H5N1=AS03-021.
- PMR # 4: Deferred pediatric study Q-Pan-025 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy infants < 6 months of age.

The original pediatric plan was developed considering data in children 6 months to < 36 months of age who received related pandemic H1N1 influenza vaccines adjuvanted with AS03 (Arepanrix and Pandemrix, Table 1). In this age group, relatively high rates of solicited adverse reactions (e.g., injection site pain, irritability, fever) were observed after the second vaccine dose. These data suggested that a lower dose of the Q-Pan H5N1 vaccine may be needed in the pediatric age group. While the first pediatric study, Q-PAN H5N1=AS03-021, evaluated half of the adult dose in persons 6 months to < 18 years of age, additional studies were planned to assess the potential need for a lower dose. Q-Pan-023 was initially planned as a dose finding study to evaluate the safety and immunogenicity of Q-Pan H5N1 when administered to healthy children 6 months to < 36 months of age. Moreover, study Q-Pan-024 was tentatively proposed to evaluate the safety and immunogenicity of a lower dose of Q-Pan H5N1 when administered to healthy persons 6 months to < 18 years of age. Study Q-Pan-024 was to be conducted only if study Q-Pan-023 identified a pediatric dose that was different than that evaluated in study Q-Pan H5N1=AS03-021.

On September 8, 2014, a meeting was held between CBER and GSK to address GSK's overall pediatric study plan that was part of the postmarketing pediatric requirements for the Q-Pan H5N1 BLA. During this meeting, CBER indicated that based on the preliminary review of the immunogenicity and safety data from study Q-PAN H5N1=AS03-021 submitted to BB-IND

13413, conducting additional dose-ranging studies in children 6 months to < 18 years of age was not necessary as the existing immunogenicity and safety data from this study may be adequate to support submission of a supplemental application for licensure of Q-Pan H5N1 for use in persons 6 months to < 18 years of age. During the same meeting, CBER and GSK also discussed the PREA-required study Q-Pan-025 to evaluate the Q-Pan H5N1 vaccine in infants less than 6 months of age. GSK indicated that this study was not feasible in the absence of a pandemic, and proposed to submit a protocol that would be ready to be implemented in the event of a pandemic. CBER agreed that a “shelf-ready” protocol would be desirable in the event of a pandemic and recommended that the company submit a proposal for a change in the milestone dates in the BLA supplement for our evaluation.

Subsequently, GSK submitted a pediatric BLA supplement for Q-Pan H5N1, which is the subject of this SBRA. As described above, the submission includes safety and immunogenicity from study Q-Pan H5N1=AS03-021 (PMR # 1). The supplement also includes data from study Q-Pan H1N1-035. Furthermore, the supplement includes a draft protocol for study Q-Pan H5N1=AS03-025 to be conducted in infants less than six months of age (this study is also designated Q-Pan-025 in PMR # 4, listed above). As discussed during the meeting previously mentioned, in this supplement GSK requested a change in the timeline for PMR # 4 so that the study may “be conducted in the event of an imminent H5N1 influenza virus pandemic (human to human H5N1 transmission).” In addition, the supplement provides revised labeling [Prescribing Information (PI), carton, and vial], a revised Pharmacovigilance Plan, and updated validation data for the [REDACTED] assay.

3. Chemistry Manufacturing and Controls (CMC) and Clinical Serological Assay Information

No manufacturing changes were proposed for this supplement; thus, no manufacturing information was submitted in this supplement.

GSK submitted additional validation information and bridging-related documents in this supplement because several changes were implemented in the [REDACTED] assay and there was a change in laboratories (i.e., the test was transferred from Dresden to [REDACTED]) since the initial BLA submission. In the Q-PAN H5N1=AS03-021 study, description of the immune response of Q-Pan H5N1 in terms of [REDACTED] titers specific for the vaccine-homologous virus and for a drift-variant strain was a secondary immunogenicity objective. Testing of the Q-PAN H5N1=AS03-021 clinical samples was conducted in the [REDACTED]. Dr. Hana Golding and Dr. Rong Fu reviewed the updated validation information for the [REDACTED] assay submitted to the supplement. Overall, both reviewers concluded that the validation data were acceptable to support use of the [REDACTED] assay for its intended purpose in study Q-PAN H5N1=AS03-021. Of note, results of the [REDACTED] assay were not considered part of the basis for the regulatory action and, therefore, are not discussed further in this document.

4. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology or toxicology information was submitted in this supplement.

5. Clinical Pharmacology

No clinical pharmacology or pharmacokinetic data were submitted in this supplement.

6. Clinical/Statistical

a) Clinical Program: Pediatric Age Group 6 Months Through 17 Years

Q-PAN H5N1=AS03-021 was a randomized, placebo-controlled, observer-blind, multicenter trial conducted in the U.S., Canada, and Thailand. In this study, 838 subjects were randomized in an 8:3 ratio and stratified by age (6 through 35 months, 3 through 8 years, and 9 through 17 years) to receive either Q-Pan H5N1 (n = 607) or a saline placebo (n = 231). Each group received a 2-dose series administered 21 days apart. Analyses of age groups 6 through 35 months (mean: 22 months), 3 through 8 years (mean: 6 years), and 9 through 17 years (mean: 13 years) were conducted. Hemagglutination-inhibition (HI) antibody titers to the A/Indonesia/05/2005 (H5N1) strain were evaluated in sera obtained 21 days after the second dose with Q-Pan H5N1 or placebo.

The primary endpoint was the proportion of subjects with HI antibody titers of $\geq 1:40$ after vaccination for the hemagglutinin (HA) antigen. The pre-specified criterion for success was a lower bound for the 98.3 % confidence interval ≥ 70 % for any age stratum. Each age stratum was evaluated independently. Serum HI antibody responses to Q-Pan H5N1 met the pre-specified criteria for all age strata (Table 2)

Table 2. Percentage of Subjects with HI Titers $\geq 1:40$ following Q-Pan H5N1 or Placebo (21 Days after Dose 2) (ATP Cohort for Immunogenicity at Day 42)

Age Group	Q-Pan H5N1		Placebo	
	n	% (98.3% CI)	n	% (98.3% CI)
Subjects 6 through 35 months	175	100.0 ^a (97.3, 100.0)	64	0 (0, 7.2)
Subjects 3 through 8 years	184	99.5 ^a (96.3, 100)	71	0 (0, 6.5)
Subjects 9 through 17 years	203	99.0 ^a (95.8, 99.9)	76	1.3 (0, 8.6)

HI = Hemagglutination-inhibition; ATP = According-to-protocol; CI = Confidence Interval.

n = Number of subjects with available results.

ATP cohort for immunogenicity included a subset of subjects who received 2 doses of vaccine and had serum collections according to the protocol.

^aFor the proportion of subjects with HI antibody titers of $\geq 1:40$ after vaccination, the pre-specified target was met based on a lower bound for the 2-sided 98.3% confidence interval ≥ 70 % for all 3 age strata.

Bioresearch Monitoring Review: The Bioresearch Monitoring (BIMO) Branch issued inspection assignments covering three clinical investigator sites for study Q-PAN H5N1=AS03-021 (Protocol 114464). The clinical sites were selected based on several factors, including subject enrollment, previous inspectional history, geographic location, and reported potential

immune-mediated disease with an unclear diagnosis. Protocol 114464 (Q-PAN H5N1=AS03-021) was conducted at a total of 17 study sites: 11 sites in the U.S. and 6 sites outside of the U.S. The three sites selected represented approximately 46 % of the enrolled subjects. The BIMO inspection results from the aforementioned study sites did not reveal problems that impact the data submitted in the application (Table 3).

Table 3. Inspections of Clinical Sites and Outcome

Site Number	Site Location	Country	Form FDA 483 Issued	Final Inspection Classification
85912	Kentucky Pediatric/Adult Research Bardstown, Kentucky	U.S.	No	No Action Indicated
85917	Benchmark Research Fort Worth, Texas	U.S.	No	No Action Indicated
87086	Srinagarind Hospital Khon Kaen University Khon Kaen	Thailand	No	No Action Indicated

Pediatric Research Equity Act: As mentioned above, in consultation with FDA’s PeRC, CBER deferred submission of studies for all pediatric subgroups for the original BLA because the product was ready for approval for use in adults and the pediatric studies had not been completed. The following deferred pediatric studies were cited in the November 22, 2013, approval letter as the required postmarketing pediatric studies under PREA:

- PMR # 1: Deferred pediatric study Q-Pan H5N1-AS03-021 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy persons 6 months to < 18 years of age.
- PMR # 2: Deferred pediatric study Q-Pan-023 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy children 6 months to < 36 months of age.
- PMR # 3: Deferred pediatric study Q-Pan-024 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy persons 6 months to < 18 years of age. Study Q-Pan-024 will be conducted only if study Q-Pan-023 identifies a pediatric dose that is different than that evaluated in study Q-Pan H5N1=AS03-021.
- PMR # 4: Deferred pediatric study Q-Pan-025 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy infants < 6 months of age.

The Office of Vaccines Research and Review (OVR) presented GSK’s pediatric assessment in children 6 months through 17 years of age and a change in schedule for the PREA PMR # 4 to the PeRC on July 27, 2016. OVR made the following recommendations:

- a. OVR proposed that this supplement fulfills the pediatric study requirement for persons 6 months to < 18 years of age. PMR # 1 (study Q-Pan H5N1=AS03-021) provides an assessment in the pediatric population from 6 months to < 18 years of age that is sufficient to support approval in this age group.

- b. OVRP proposed releasing GSK from PREA PMRs # 2 and # 3. As mentioned above (in *item a*), this submission is sufficient to fulfill the pediatric study requirement for persons 6 months to < 18 years of age and no additional studies are required.
- c. OVRP agreed with GSK that study Q-Pan-025 in infants < 6 months of age would only be feasible in the event of an imminent H5N1 influenza virus pandemic (human to human H5N1 transmission). OVRP noted that this is consistent with another company's agreed iPSP for a pandemic H5N1 virus vaccine for which studies in this age group are planned if sustained human to human transmission of H5N1 is documented (refer to the Pediatric Review Committee held on September 17, 2014; BB-IND 13536). OVRP agreed with GSK's proposal to remove specific milestone dates (final protocol submission, study completion, and final report submission) for PMR # 4 (study Q-Pan-025). OVRP considered this to be a change in the PREA PMR. OVRP preferred not having specific dates for PMR # 4 because the occurrence of a pandemic is unpredictable and a pandemic could occur earlier than an arbitrary date.

The PeRC agreed with the recommendation that Q-Pan H5N1 has been fully assessed in persons 6 months to < 18 years of age. They also agreed that PMR # 1 has been fulfilled and that GSK could be released from PMRs # 2 and # 3 because the studies are no longer necessary. Furthermore, the committee agreed with the recommendation to change the schedule for PMR # 4 making the timeline contingent upon an imminent H5N1 influenza virus pandemic (human to human H5N1 transmission).

PEDIATRIC REQUIREMENTS

Based on the PeRC discussion, the status of GSK's postmarketing requirements identified in the November 22, 2013, approval letter under STN 125419/0 has been updated to reflect the following:

- **Fulfillment of Pediatric Postmarketing Requirement (PMR # 1):** GSK has fulfilled the pediatric study requirement for ages 6 months to < 18 years for this application.
- **Release from Pediatric Postmarketing Requirements (PMRs # 2 and # 3):** This submission is sufficient to fulfill the pediatric study requirement for ages 6 months to < 18 years and no further studies are required. PMRs # 2 and # 3 are considered closed.
- **Change in Schedule for Pediatric Postmarketing Requirement:** The timeline is revised for PMR # 4. GSK requested a change in the milestone dates because it would not be feasible to conduct the study in the absence of an H5N1 influenza virus pandemic.

7. Clinical Safety

As described above in Section 6: *Clinical/Statistical*, study **Q-PAN H5N1=AS03-021** was a randomized, placebo-controlled, observer-blind, multicenter trial, in which 838 subjects (6 months through 17 years of age) were randomized in an 8:3 ratio to receive Q-Pan H5N1 (n = 607) or saline placebo (n = 231) as a 2-dose vaccination series. In the overall population, the mean age was 7 years (range: 6 months through 17 years); 52 % were male; 45 % were white, 15 % black, 36 % Asian, and 4 % other racial groups; 11 % were Hispanic or Latino. An uncontrolled crossover study was subsequently conducted in which 155 subjects who initially received placebo, then received Q-Pan H5N1 as a 2-dose series.

The most common solicited local reaction reported was injection site pain, reported by 47 % of subjects 6 through 35 months, 71 % of subjects 3 through 8 years, and 82 % of subjects 9 through 17 years. In the placebo group, injection site pain was reported in 30 %, 38 %, and 23 % of subjects in these age groups, respectively. The most frequently reported systemic solicited reactions were irritability and myalgias. Irritability was reported by 51 % of subjects 6 through 35 months, and 30 % of subjects 3 through 5 years. In the placebo group, irritability was reported in 40 % and 22 % of subjects, respectively. Myalgias were reported by 35 % of subjects 6 through 8 years, and 42 % of subjects 9 through 17 years. In the placebo group, myalgias were reported in 19 % and 15 % of subjects, respectively.

The incidences of unsolicited adverse events reported during the 21-day post-vaccination periods for subjects who received Q-Pan H5N1 or placebo were 39 % and 42 %, respectively. Events reported in the Q-Pan H5N1 group at a rate of ≥ 0.5 % of subjects and at a rate at least twice that of the placebo group were all injection site reactions combined (1.6 % Q-Pan H5N1 vs. 0.4 % placebo), gastroenteritis (1.2 % Q-Pan H5N1 vs. 0.4 % placebo), eye infections (1.0 % Q-Pan H5N1 vs. 0.4 % placebo), varicella (0.7 % Q-Pan H5N1 vs. 0 % placebo), and fatigue (0.5 % Q-Pan H5N1 vs. 0 % placebo).

During the approximately one-year safety follow-up (Day 385), Serious Adverse Events (SAEs) were reported for 8 (1.3%) subjects who received Q-Pan H5N1, and for 4 (1.7%) subjects who received placebo. Most of these SAEs were identified after the second dose. Only one SAE, febrile convulsion, was reported on Day 11 following the first vaccine dose in a 30-month-old subject who received Q-Pan H5N1; although no fever occurred during the first 7 days post-vaccination, febrile convulsion is noted due to the temporal association with vaccination and because no alternative plausible cause for the event was identified.

Based on a pre-specified list of potentially immune-mediated disease, one case of alopecia was reported through Day 385 in a subject who received Q-Pan H5N1 and one case of Type 1 diabetes was reported in a subject who received placebo.

As mentioned above, 155 subjects who initially received placebo, received a 2-dose series of Q-Pan H5N1 in the crossover study. Two (1.3%) subjects reported SAEs, which were not related to vaccination, through the one-year safety follow-up (Day 385). No potential immune-mediated diseases were reported.

In addition to the safety experience accrued with study Q-PAN H5N1=AS03-021, CBER reviewed the safety data from study **FLU Q-Pan H1N1-035** in support of licensure of Q-Pan H5N1 in the pediatric population. This was a randomized, controlled, observer-blind, multicenter trial. This study was conducted in 8 countries (Australia, Brazil, Colombia, Costa Rica, Mexico, Philippines, Singapore, and Thailand). A total of 6,145 subjects 6 months through 9 years of age were randomized 1:1:1 to receive: one dose of Q-Pan H1N1, two doses of Q-Pan H1N1 administered 21 days apart, or two doses of a non-US licensed unadjuvanted influenza A (H1N1) virus vaccine (manufactured by GSK) administered 21 days apart.

SAE rates in subjects who received the adjuvanted vaccine (one or two doses) and the unadjuvanted vaccine were similar. The following SAEs reported through Day 385 in subjects who received the adjuvanted vaccine are noted because no alternative plausible causes for the event were identified or due to the temporal association with vaccination. One death was reported within 42 days of any vaccination: a 6-month-old with a prior episode of pneumonia developed symptoms described as pneumonia and asthma exacerbation beginning on Day 7

following the first dose of the adjuvanted vaccine and died of sepsis on Day 19. The following non-fatal SAEs were reported through Day 385: hepatitis and nasopharyngitis on Day 5 following vaccination (1 subject), appendicitis on Days 8 or 9 following vaccination (3 subjects), and papillary thyroid cancer on Day 84 following vaccination (1 subject).

Based on a pre-specified list of events, 7 subjects (0.2 %) in the adjuvanted arms (n = 4,096) reported new-onset potential immune-mediated diseases through Day 385; 4 subjects (0.2 %) in the unadjuvanted arms (n = 2,049) reported such events. Events reported following administration of the adjuvanted vaccine were alopecia areata (2 subjects), glomerulonephritis (2 subjects), hypothyroidism (2 subjects), and idiopathic thrombocytopenic purpura (1 subject). Events reported following administration of the unadjuvanted vaccine were glomerulonephritis (2 subjects), Guillain-Barré syndrome (1 subject), and erythema multiforme (1 subject).

Although Q-Pan H5N1 was approved in 2013, there is no postmarketing experience available for the vaccine because it has not been used (outside of the pre-licensure clinical trials). Q-Pan H5N1 was developed under contract to the U.S. Government as part of national pandemic preparedness initiatives and GSK does not intend to market the vaccine for commercial distribution in the U.S. Nevertheless, two AS03-adjuvanted vaccines, Pandemrix and Arepanrix (Table 1), were administered outside the U.S. in 2009 during the mass vaccination campaigns conducted during the H1N1 influenza virus pandemic. The Q-Pan H5N1 vaccine and Arepanrix are both AS03-adjuvanted vaccines manufactured according to the FluLaval process licensed in the U.S. Pandemrix is an AS03-adjuvanted vaccine manufactured by GSK in Dresden, Germany, using an alternative manufacturing process (i.e., the Fluarix process, which is also licensed in the U.S., refer to Table 1).

Narcolepsy has been reported following administration of Pandemrix during the 2009 mass vaccination campaigns during the H1N1 pandemic, although it has not been reported in clinical trials involving Q-Pan H5N1 vaccination. In Finland and Sweden, increases in the rate of diagnoses of narcolepsy were noted in children following the immunization campaign. Multiple follow-up studies were conducted, some of which showed increases in risk associated with the vaccine. Studies in Sweden, Norway, Ireland, England, and France described significant increases in risk associated with the vaccine. The reported estimated relative risks, odds ratios, or incidence rate ratios ranged from 2 to 16. The increased risk was seen primarily in children. The relevance of these findings on narcolepsy to the U.S. population or to the Q-Pan H5N1 vaccine is unknown.

Arepanrix was used in Canada during the 2009 H1N1 influenza virus pandemic. No signal of an association between the vaccine and narcolepsy was noted during the active monitoring period. GSK sponsored a study in Québec that has shown highly variable results. The Office of Biostatistics and Epidemiology (OBE) noted that among the multiple analyses in this study, the cohort analysis conducted in the province of Québec, Canada, using a 16-week risk window for the study period between May 1, 2009, and March 31, 2010, was the least biased and did not identify a statistically significant increased risk. Moreover, OBE conducted a literature review to identify additional epidemiological evidence which would contribute to the existing knowledge on the use of adjuvanted influenza vaccine and narcolepsy. The OBE reviewer did not identify additional information that would change the risk assessment.

In addition, reports of autoimmune hepatitis (AIH) have occurred in the postmarketing setting in association with Pandemrix. No AIH cases were spontaneously reported subsequent to

Arepanrix administration. Two cases of AIH were reported in clinical studies, including one from a study conducted in adults with Q-Pan H5N1 (in study FLU Q-PAN-002, not the subject of this pediatric clinical program) and one pediatric subject from a clinical study conducted with the investigational D-Pan H5N1 vaccine.

8. Advisory Committee Meeting

This supplement did not require input from the Vaccines and Related Biological Products Advisory Committee.

9. Other Relevant Regulatory Issues

There were no additional relevant issues.

10. Labeling

GSK submitted revised versions of the PI as well as carton and container labels as a result of comments provided by CBER during labeling negotiations. The revised PI and carton/container labels were evaluated by the review committee.

GSK added linear barcodes to the draft antigen container label, the antigen carton label, the adjuvant carton label, and the adhesive-backed label (*shoebox* - front and back) intended for use on the outer carton's panels. GSK also made changes to the draft carton label, *shoebox* - front, as follows:

- Revisions to the dosage statement
- Revisions to the dose content
- Update to the storage statement

Changes recommended and negotiated for the PI included:

- Addition of safety and immunogenicity data from study Q-Pan H5N1=AS03-021 to support use of Q-Pan H5N1 in the pediatric population (6 months through 17 years of age)
- Description of solicited reactions by subject age and using a more conservative grading scale for measurable local injection site reactions that is more appropriate for a young pediatric population
- Adding relevant safety data from the uncontrolled crossover portion of study Q-Pan H5N1=AS03-021 (Year 2)
- Inclusion of an SAE with a temporal association and no alternative plausible cause, as is consistent with the adult section of the PI
- Adding relevant safety data from study FLU Q-Pan H1N1-035, which evaluated Q-Pan H1N1, a related AS03-adjuvanted influenza virus vaccine manufactured using the same processes as Q-Pan H5N1
- Revisions to the Pregnancy and Lactation sections as required by the Pregnancy and Lactation Labeling Rule
- Adjustment of immunogenicity results to reflect data from the pre-specified, according to protocol population

- Addition of “paresthesia” under Section 6.2: *Postmarketing Experience*. CBER recommended the addition of this term based on a report from Canada, in which a passive surveillance system identified paresthesia as the third-most-common adverse event, after allergic-like symptoms and local reactions, for vaccines administered between October 26 and December 31, 2009.

11. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

Q-Pan H5N1 was licensed via the “traditional” approval pathway on November 22, 2013, for use in persons 18 years of age and older. Pre-licensure clinical trials evaluated the safety and immunogenicity of Q-Pan H5N1. While a clinical endpoint efficacy study of Q-Pan H5N1 was not feasible, effectiveness of Q-Pan H5N1 was inferred from the clinical efficacy of FluLaval Quadrivalent (Table 1). FluLaval Quadrivalent is a U.S.-licensed unadjuvanted seasonal inactivated influenza vaccine that was approved in August 15, 2013, for use in persons 3 years of age and older via the “traditional” approval pathway. The manufacturing process used for the production of the Q-Pan H5N1 is the same as for the seasonal vaccine, FluLaval Quadrivalent.

As described above in Section 6: *Clinical/Statistical*, GSK conducted a randomized, placebo-controlled, observer-blind, multicenter trial in which subjects were stratified by age (6 through 35 months, 3 through 8 years, and 9 through 17 years) to receive either Q-Pan H5N1 or a saline placebo. The primary endpoint was the proportion of subjects with serum HI antibody titers of $\geq 1:40$ after vaccination. The pre-specified criterion for success was a lower bound for the 98.3% confidence interval $\geq 70\%$ for any age stratum. Each age stratum was evaluated independently. Serum HI antibody responses to Q-Pan H5N1 met the pre-specified criteria for all age strata (the lower bound for the 98.3 % confidence interval was $> 95\%$ for each age stratum, Table 2). The data included in this BLA supplement support “traditional” approval of use of Q-Pan H5N1 in persons 6 months of age and older.

The review committee recommends approval of this BLA supplement to include safety and effectiveness data to support use of the Q-Pan H5N1 vaccine in persons 6 months through 17 years of age.

b) Risk/Benefit Assessment

In view of the submitted data to support the safety and effectiveness of the Q-Pan H5N1 vaccine that have been presented and discussed in this document, as well as the high degree of morbidity and mortality associated with H5N1 influenza virus illness, the review committee is in agreement that the risk/benefit profile for the Q-Pan H5N1 vaccine is favorable with respect to the intended indication and usage.

c) Recommendation for Postmarketing Risk Management Activities

There was no recommendation for any *Risk Evaluation and Mitigation Strategies*. See below for the postmarketing activities associated with the licensure of this product.

d) Recommendation for Postmarketing Activities

As discussed in Section 6: *Clinical/Statistical*, GSK is required to conduct postmarketing pediatric studies in accordance with PREA under Section 505B(a) of the Federal Food, Drug, and Cosmetic Act. This supplement contains a fulfillment of a pediatric postmarketing

requirement for ages 6 months to < 18 years. The supplement also includes a change in schedule for a pediatric postmarketing requirement to evaluate the immunogenicity and safety of Q-Pan H5N1 in infants less than 6 months of age (PMR # 4).

OBE reviewed and found GSK's proposed Pharmacovigilance Plan acceptable, once certain recommended modifications were made. OBE also reviewed GSK's proposal to conduct an active surveillance postmarketing pandemic cohort study as well as the concept protocol for the pregnancy registry and found them acceptable.

In addition, GSK has agreed to the following adverse event reporting when the Q-Pan H5N1 vaccine is used:

To report all serious or non-serious cases of narcolepsy (with or without cataplexy), autoimmune hepatitis, anaphylaxis, Bell's palsy, convulsion, demyelinating disorders, encephalitis, Guillain-Barré syndrome, neuritis, vasculitis, and vaccination failure, following vaccination with Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, as 15-day expedited reports to the Vaccine Adverse Event Reporting System (VAERS).