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Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Biostatistics and Epidemiology  
Division of Biostatistics

## STATISTICAL REVIEW AND EVALUATION BLA

**BLA/Supplement Number:** 125419.0

**Product Name:** Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted

**Indication(s):** Active immunization for the prevention of disease in persons 18 years of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine

**Applicant:** ID Biomedical Corporation of Quebec / GSK Biologicals

**Date of Submission:** February 22, 2012

**Action Due Date:** March 23, 2013

**Review Priority:** Standard

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## 1. EXECUTIVE SUMMARY

BLA 125419 was submitted by GSK for the AS03 adjuvanted Influenza A (H5N1) Virus Monovalent Vaccine manufactured in Quebec (also referred to as Q-Pan H5N1) indicated for the prevention of disease in persons 18 years of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

Reports of two pivotal immunogenicity studies (Q-Pan-001 and Q-Pan-002) conducted with Q-Pan H5N1 vaccine, one pivotal observational effectiveness study conducted with Q-Pan H1N1 vaccine (Van Buynder study), and two Integrated Summary of Safety (ISS) analyses are reviewed.

**Immunogenicity:** Based on studies Q-Pan-001 and Q-Pan-002, the candidate H5N1 vaccine with AS03 adjuvant appears to be immunogenic. The criteria of SCR (lower bound of 95% CI  $\geq$  40% for 18-64 years and  $\geq$  30% for >64 years) and SPR (lower bound of 95% CI  $\geq$  70% for 18-64 years and  $\geq$  60% for >64 years) are well met. The benefit of the adjuvant AS03 is demonstrated in study Q-Pan-001, and clinical lot consistency is demonstrated in study Q-Pan-002.

**Effectiveness:** Although the results of the Van Buynder study may suggest that the Q-Pan H1N1 vaccine, *Arepanrix*, was effective in preventing H1N1 influenza during the 2009/2010 H1N1 pandemic in children 6 months to <10 years of age, as the only pivotal effectiveness study, this small, retrospective, case-control observational study has too many limitations to provide a reliable VE estimate to support traditional approval of Q-Pan-005.

**Safety:** The AS03 adjuvanted Q-Pan H5N1 vaccine appears to have increased local and general reactogenicity compared to placebo or H5N1 antigen alone, particularly local injection site pain. No notable imbalance was found for medically-attended AEs (MAEs), serious AEs (SAEs), and AEs of special interest (AESIs) which are not potentially immune-mediated disorders (pIMDs). The Integrated Summary of Safety (ISS) analyses results showed an increased relative risk (RR) for pIMDs in adjuvanted H5N1 recipients, but not in adjuvanted H1N1 recipients. However, ISS results should be interpreted with caution due to many limitations in such a pooled analysis.

Considering the immunogenicity demonstrated and the antigen-sparing advantage highly desired in a pandemic situation, the clinical benefit of Q-Pan H5N1 for pandemic use or for adults at increased risk of exposure to H5N1 virus appears to outweigh the risk of increased reactogenicity and potential increase of pIMDs incidence. However, due to the differences between the Day 182 and Day 364 safety datasets of Study Q-Pan-002 identified by the clinical reviewer, the review team decided that submission of the complete study data package for FLU Q-Pan-002 was warranted in order to make an appropriate regulatory decision.

## 2. INTRODUCTION

GSK filed BLA 125419 to seek licensure for their AS03 adjuvanted Influenza A (H5N1) Virus Monovalent Vaccine manufactured in Quebec (also referred to as Q-Pan H5N1). To support the efficacy of Q-Pan H5N1, the applicant presented the following pivotal and supportive studies:

- **Pivotal Immunogenicity Studies Conducted with Q-Pan H5N1 Vaccine**

**Q-Pan-001:** a randomized, observer-blind, multi-center, phase I/II study to evaluate the immunogenicity and safety of Q-Pan H5N1 administered intramuscularly (IM) in adults 18 to 64 years of age in the US and Canada. This study was conducted at 10 sites, including 7 sites in the US and 3 in Canada.

**Q-Pan-002:** a Phase III, observer-blind, saline placebo-controlled, multi-center study designed to evaluate the safety and immunogenicity of a 2-dose series of Q-Pan H5N1 administered IM in adults aged  $\geq 18$  years. Three consistency lots of vaccine antigen and AS03 were provided. This study was conducted at 30 sites in the US and 10 in Canada.

- **Pivotal Effectiveness Study Conducted with Q-Pan H1N1 Vaccine**

**Van Buynder Arepanrix (Q-Pan H1N1) Study** (effectiveness study): carried out by the New Brunswick Department of Public Health, utilized a retrospective cohort, community-based case-control test-negative design. The cohort for analysis of vaccine effectiveness consisted of 91 male and female children, 6 months to  $< 10$  years of age, who had a nasopharyngeal sample tested for H1N1 infection by RT-PCR assay.

- **Supportive Q-Pan H5N1 Immunogenicity Studies**

**Q-Pan-001, Contingency Arms:** The 'contingent' portion of Study Q-Pan-001 used lower doses of H5N1 antigen A/Indonesia/5/2005.

**Q-Pan-005:** a Phase II, observer-blind, saline placebo-controlled multicenter study with 7 parallel groups (total  $n=840$ ) to assess whether a single booster dose of H5N1 vaccine adjuvanted with AS03 is more immunogenic when given to subjects who 6 or 18 months previously received a single priming dose of a heterologous H5N1 vaccine than when given to H5N1-naïve subjects.

**Q-Pan-009:** a Phase II, randomized, open-label, multi-center study with 4 parallel groups. The study was carried out in 312 adults 18 to 64 years of age in Canada to evaluate the immunogenicity of accelerated primary vaccination with Q-Pan H5N1 vaccine.

**Q-Pan-010:** a Phase II, randomized, parallel group, observer-blind, multi-centered, single booster dose study in veterans of study Q-Pan-001 to compare immunogenic priming induced by a two-dose series of H5N1 antigen, administered alone or in combination with two different doses of AS03.

- **Supportive Arepanrix (Q-Pan H1N1) Effectiveness Studies**

**Mahmud Study:** a population based case control study using data from Cadham Provincial Laboratory (CPL) and the Manitoba Immunization Monitoring System (MIMS). All Manitoba residents  $\geq 6$  months of age who had a respiratory specimen tested at CPL for

H1N1 were included in the study. Cases were individuals who tested positive for H1N1 by reverse transcriptase-PCR (N=1435). Controls were individuals who tested negative for both influenza A and B (N=2309). Among them, 114 cases and 438 controls received *Arepanrix*.

**Skowronski Study:** a test negative incident case control study based on a sentinel physician surveillance system. The study population consisted of 552 patients who presented to a sentinel site within seven days of onset of influenza-like illness between 8 November and 5 December 2009; participants were mostly (> 80%) less than 50 years old (with the youngest participants being children 6 months old).

The applicant was not able to obtain the data and study documents for the Mahmud and Skowronski studies. Only the published articles were submitted.

This review will focus on the two pivotal immunogenicity studies (Q-Pan-001 and Q-Pan-002), the pivotal effectiveness study (Van Buynder *Arepanrix* study), and the Integrated Summary of Safety (ISS) reports.

### 3. STATISTICAL EVALUATION

#### 3.1 STUDY Q-PAN-001

**Study Title:** A phase I/II, observer-blind, randomized, active-controlled trial to evaluate the safety and immunogenicity of a two-dose series of monovalent H5N1 vaccine antigens without adjuvant and with two different strengths of AS03.

The study was conducted in 2007 at 10 study centers, including 7 in the US and 3 in Canada.

#### **Objectives:**

##### *Primary:*

- To demonstrate the adjuvant activity of AS03 by comparing the immunogenicity of the Q-Pan H5N1 antigen at the 3.8 µg dose level with AS03 at two different strengths (full, AS03<sub>A</sub>, and half, AS03<sub>B</sub>) versus that of Q-Pan H5N1 antigen alone at the 3.8 µg dose level.
- To describe the safety of Q-Pan H5N1 antigen at the 3.8 µg dose level with full and half strength AS03 in terms of solicited local and general reactogenicity events, unsolicited adverse events (AEs), and serious adverse events (SAEs) in comparison to antigen alone.

##### *Secondary:*

- To describe the immunogenicity of Q-Pan H5N1 antigen at the 3.8 µg dose level with full and half strength AS03 in terms of the incidence rate of homologous virus hemagglutination-inhibition (HI) seroconversion, the frequency of attainment of potentially “seroprotective” HI reciprocal titers of  $\geq 40$ , the geometric mean fold-rise (GMFR) in HI titers and HI geometric mean titers (GMTs).

- To assess the equivalence, based on vaccine-homologous virus HI GMTs, of H5N1 vaccine antigen manufactured in Quebec (Q-Pan) administered with AS03 and H5N1 vaccine antigen manufactured in Dresden (D-Pan) administered with AS03.
- To describe the comparative safety of Q-Pan H5N1 vaccine antigen administered with AS03 and D-Pan H5N1 vaccine antigen administered with AS03.
- To further describe immunogenicity of selected vaccine regimens in terms of vaccine homologous virus microneutralization titers and both HI and microneutralization titers against one or more H5N1 drift variant virus strains.

### 3.1.1 Study Design

This is a randomized, observer-blind, multi-centered, active-controlled five-arm trial. Subjects were randomized in a 1:2:2:2:2 ratio to receive two IM doses of one of the following vaccines on Days 0 and 21:

**Table 1 Study Design, Q-Pan-001**

Group	A/Indonesia/5/05 H5N1 Antigen dose	Adjuvant strength	N planned	N enrolled
A (Q-unadj)	Q-Pan 3.8 µg	-	75	78
B (Q-AS03 <sub>A</sub> )	Q-Pan 3.8 µg	AS03 <sub>A</sub>	150	152
C (Q-AS03 <sub>B</sub> )	Q-Pan 3.8 µg	AS03 <sub>B</sub>	150	151
D (D-AS03 <sub>A</sub> )	D-Pan 3.8 µg	AS03 <sub>A</sub>	150	151
E (D-AS03 <sub>B</sub> )	D-Pan 3.8 µg	AS03 <sub>B</sub>	150	148
Total			675	680

Randomization was stratified by site and age (18 – 40 years and 41 – 64 years) where no more than 60% of subjects fell into one age stratum.

Based on an analysis concerning immunogenicity performance at Day 42 in Groups B and C above, supplemental treatment groups could be assessed in contingency treatment arms. Such testing, using a lower H5N1 antigen dose, was in fact triggered by the results.

#### **Endpoints:**

#### **Immunogenicity:**

*Primary:* HI titer against vaccine-homologous virus at Day 42 (2 weeks post 2<sup>nd</sup> dose)

*Secondary:* HI titer against vaccine-homologous virus at Day 21 (post 1<sup>st</sup> dose) and Day 182.

**Safety:** The primary safety endpoints are:

- The occurrence of specifically-solicited local and general signs and symptoms during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after each dose of vaccine and overall per subject considering both post-immunization periods.

- The occurrence of unsolicited AEs during a 21-day follow-up period after the first vaccination and 21 days after the second vaccination (Day 0 to 21 pre-dose and Day 21 post-dose to Day 42 intervals), as well as overall (Day 0 through Day 84).
- The occurrence of SAE(s), medically-attended events, and new onset chronic diseases during the entire study period (Day 0 to 182).

### **3.1.2 Statistical Methods**

#### **Analysis Populations:**

- According to Protocol cohort for immunogenicity analysis (ATP-I) – All evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom a complete set of data concerning immunogenicity endpoint measures required for the primary endpoints were available.
- According to Protocol cohort for immunogenicity analysis (ATP-S) – All subjects who had received at least one dose of study vaccine/comparator according to their random assignment, with sufficient data to perform an analysis of safety, had not received a vaccine forbidden in the protocol or other protocol-excluded medications, and for whom the randomization code had not been broken, unless the unblinding was required due to SAE.
- Total Vaccinated cohort (TVC) – All subjects who received at least one dose of vaccine for whom any post-vaccination data were available.

#### **Immunogenicity Analyses:**

Primary immunogenicity analyses were performed on the ATP-I cohort. Seroconversion rate (SCR) was defined as the percentage of vaccinees who had either a pre-vaccination (Day 0) titer <10 and a post-vaccination titer  $\geq 40$  or a pre-vaccination titer  $\geq 10$  and at least a 4-fold increase in post-vaccination titer. Rate of HI Titers  $\geq 40$  (potential seroprotection rate, SPR) was defined as the percentage of all vaccinees with a HI antibody titer  $\geq 40$ . Geometric Mean Fold-Rise (GMFR) was defined as the geometric mean of the within-subject ratios of the post-vaccination HI titer to the Day 0 HI titer.

The primary immunogenicity analyses were the GMT ratio of antibody against the H5N1 antigen and the difference in SCR, for adjuvanted Q-Pan H5N1 as compared to Quebec-manufactured H5N1 antigen alone. Superiority of the adjuvant formulation was to be established if the lower bound of the 95% confidence interval (CI) on the GMT ratio exceeded 2.0 and the lower bound of the 95% CI on the difference in SCR exceeded 15%. Statistical tests were to be performed sequentially for adjuvant effect, first for a full-dose adjuvant effect by testing Group B versus Group A, followed by a test for half-dose adjuvant effect (Group C versus Group A). Each test was to be performed at the one-sided,  $\alpha=0.025$  level of significance. For the analysis of differences in SCR, Miettinen and Nurminen's method of calculation of an approximate 95% confidence interval for the SCR difference was used. The 95% confidence interval for the ratio of GMTs was calculated, based on an approximately normal distribution of the difference in the log (base 10) of the GMTs. An analysis of covariance model with treatment group as a fixed

factor, and age strata and baseline antibody titers as covariates, was used to analyze the log10 transformed HI titers.

SPR and GMFR also were calculated, descriptive statistics tabulated, and treatment groups compared with 95% CIs.

The analysis of the equivalence of the Quebec and Dresden sources of antigen (one of the secondary objectives) was performed by analysis of variance on the log10 transformed reciprocal HI titers at Day 42, with treatment group as a fixed factor, and age strata and baseline antibody titers as covariates. The analysis used data from Groups B, C, D, and E. A 95% CI on the Group B plus Group C versus Group D plus Group E mean difference in log10 titers was calculated, and the anti-log of these limits used to calculate the CI on the GMT ratio. If these limits were between 0.67 and 1.5, equivalence was demonstrated.

**Safety Analyses:** Counts and proportions of subjects in each vaccine group with solicited reactogenicity data were tabulated by severity grade of each local and general reactogenicity event and, separately, by the total number of days in the reactogenicity interval (Days 0 to 6) with a non-zero severity grade for each category of solicited reaction. Descriptive summaries by vaccine group included the proportion (with 95% CI) of subjects with each solicited event, the mean, median, 75th, 90<sup>th</sup>, and 95th percentiles of total days with any non-zero severity grade.

Counts and proportion of subjects with unsolicited AEs reported up to 21 days after each vaccination, and overall (Days 0 through 84), were tabulated and included standardized asymptotic 95% CIs. Tabulations were produced for all AEs, in addition to those that were vaccine-related, Grade 3 (severe), and both Grade 3 and vaccine-related. AEs were coded and summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and preferred term. Data were displayed by vaccine group within age stratum and across both age strata.

### 3.1.3 Disposition of Subjects

**Table 2 Subject Enrollment and Disposition, Q-Pan-001**

Title	Total	Q-unadj	Q-AS03A	Q-AS03B	D-AS03A	D-AS03B
	N (%)	n	n	n	n	n
Total enrolled cohort	680	-	-	-	-	-
Total vaccinated cohort	680 (100%)	78	152	151	151	148
ATP safety cohort	672 (98.8%)	78	149	149	149	147
ATP immunogenicity cohort	648 (95.3%)	75	144	146	140	143

n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number

% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Source: Table 12 in the applicant's Clinical Study Report

Seven enrolled subjects did not complete the Day 42 analysis: six subjects withdrew from the study as a result of consent withdrawal and 1 subject moved outside the study area; no subject withdrew from the study due to an adverse event or protocol violation. All enrolled subjects

received at least 1 dose of study vaccine. Of the 680 enrolled subjects, 15 (2.2%) subjects received only 1 dose of vaccine and 665 (97.8%) subjects received 2 doses of vaccine. Subjects with protocol deviations leading to exclusion from the ATP-I cohort were mostly due to non-compliance with vaccination schedule, including outside protocol-specified window or wrong and unknown dates.

### 3.1.4 Demographics Characteristics

The demographic profile of the 5 groups of subjects was comparable with respect to mean age, gender, and racial distribution. The mean age of the TVC cohort was 38.6 years with 54.6% between the ages of 18 and 40 and 45.4% between the ages of 41 and 65; there were slightly more female subjects (57.8%) in the study than male subjects (42.2%); and the population was predominantly Caucasian (86.8%). The demographic information for the TVC cohort was similar to that of the ATP-I cohort.

### 3.1.5 Immunogenicity Results

**Adjuvant Effect** – To demonstrate the effect of full strength AS03 for Q-Pan H5N1, the superiority of Group B (Q-AS03<sub>A</sub>) versus Group A (Q-Pan alone) with respect to SCR and GMT at Day 42 was tested. Superiority criteria are defined as: the lower 95% confidence bound of the difference in SCR between the two groups (Group B – Group A) must be <15%, and the lower 95% confidence limit of the GMT ratio between the two groups (Group B / Group A) must be >2. The comparison results are shown in Tables 3 and 4 below:

**Table 3 Comparison of seroconversion rates at Day 42 in subjects receiving Q-Pan H5N1 with full strength adjuvant and Q-Pan H5N1 with no adjuvant, by antibody and pre-vaccination status (ATP-I), Q-Pan-001**

Antibody	Pre-vacc status	Q-AS03 <sub>A</sub> N	Q-AS03 <sub>A</sub> n	Q-AS03 <sub>A</sub> SCR %	Q-unadj N	Q-unadj n	Q-unadj SCR %	SCR Diff %	SCR Diff 95% CI LL	SCR Diff 95% CI UL
A/Indonesia	S-	144	140	97.2	75	13	17.3	79.89	69.36	87.27
A/Indonesia	S+	0	-	-	-	-	-	-	-	-
A/Indonesia	Total	144	140	97.2	75	13	17.3	79.89	69.36	87.27
A/Vietnam	S-	140	89	63.6	71	1	1.4	62.16	52.94	70.00
A/Vietnam	S+	4	0	0.0	4	0	0.0	0	-52.33	52.33
A/Vietnam	Total	144	89	61.8	75	1	1.3	60.47	51.45	68.30

S- = seronegative subjects (antibody titer < 10 1/DIL) prior to vaccination

S+ = seropositive subjects (antibody titer ≥ 10 1/DIL) prior to vaccination

N = number of subjects with pre- and post-vaccination results available

n/% = number/percentage of subjects with a vaccine response

SCR Diff = Q-AS03<sub>A</sub> minus Q-unadj

95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

Source: Table 18 of the study report submitted by the applicant

**Table 4 Comparison of adjusted ratios of GMTs at Day 42 in subjects receiving Q-Pan H5N1 with full strength adjuvant and Q-Pan H5N1 with no adjuvant, by antibody (ATP-I), Q-Pan-001**

Antibody	Q-AS03 <sub>A</sub> N	Q-AS03 <sub>A</sub> Adjusted GMT	Q-unadj N	Q-unadj Adjusted GMT	GMT ratio (Q-AS03 <sub>A</sub> /Q-unadj)	GMT ratio 95% CI LL	GMT ratio 95% CI UL
A/Indonesia	144	450	75	10.	43.40	29.93	62.94
A/Vietnam	144	40	75	5.	6.98	4.84	10.07

Adjusted GMT = geometric mean antibody titer adjusted for age stratum, baseline titer

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMT ratio (Ancova model: adjustment for age stratum, baseline titre - pooled variance);

LL = lower limit, UL = upper limit

Source: Table 19 of the study report submitted by the applicant

The effect of full strength adjuvant, Q-AS03<sub>A</sub>, was significant for both antibodies (A/Indonesia/5/05 and A/Vietnam/1194/04) when assessed by SCR and GMT. The effect of half strength adjuvant, AS03<sub>B</sub>, was also significant for both antibodies with respect to SCR and GMT. The SCR differences [Group C (Q-AS03<sub>B</sub>) – Group A (Q-unadj)] are 72.4% (95% CI 61.0-80.8%) for the A/Indonesia/5/05 antibody and 57.6% (95% CI 48.6-65.5%) for the A/Vietnam/1194/04 antibody, respectively. The adjusted GMT ratio [Group C (Q-AS03<sub>B</sub>) / Group A (Q-unadj)] was 30.0 (95% CI 20.7-43.4) for the A/Indonesia/5/05 antibody and 5.8 (95% CI 4.0-8.4) for the A/Vietnam/1194/04 antibody.

SCRs and GMTs also were compared between Groups B versus C (i.e., full strength versus half strength adjuvant). While slightly higher SCR and GMTs were seen with full strength adjuvant, the differences were not large enough to indicate superiority of the full strength adjuvant over half strength adjuvant. The adjuvant effects of Q-AS03<sub>A</sub> and Q-AS03<sub>B</sub> were further examined *post hoc* in the two age strata (18 to 40 and 41 to 64 years old). Though the criteria for adjuvant effect were met in both strata, the SCR difference and the GMT ratio between Q-AS03<sub>A</sub> and Q-AS03<sub>B</sub> were greater for the older age group. Therefore, the full strength adjuvant was selected by the applicant.

**Reviewer’s Comment:**

*Though the effect of the half strength adjuvant was not as high as the effect of the full strength adjuvant in older adults, without a clearly established correlate of protection relationship it is not known whether the immune response induced by Q-Pan H5N1 adjuvanted with half strength AS03 is or is not adequate for the older adult population. The Day 42 GMT for the 41-64 age group (Q-AS03<sub>B</sub> and D-AS03<sub>B</sub> pooled) is 209.7 with 95% CI of 160.4 to 274.2.*

**Post-Vaccination Immune Responses** – GMT, Seroconversion rate (SCR) and Proportion of Subjects attaining HI titer  $\geq$  40 (SPR)

The post-vaccination HI titer GMTs, SCR, and SPRs at Day 21 (post 1<sup>st</sup> dose), Day 42 (post 2<sup>nd</sup> dose), and Day 182 for each treatment group are presented in Table 5 below. Notable difference in GMT between the adjuvanted and unadjuvanted vaccines can be seen at Day 21 and is magnified at Day 42. CBER’s requirements for accelerated approval of pandemic influenza vaccines as described in the May 2007 guidance are: the lower bound of the 95% CI of SCR must

be  $\geq 40\%$  and the lower bound of the 95%CI of SPR must be  $\geq 70\%$ . While no treatment group met these criteria at Day 21, at Day 42 all groups receiving antigen with adjuvant (full or half-strength) achieved the recommended levels. At Day 182, the immune responses for all groups receiving adjuvanted vaccines decreased substantially from Day 42, but remained higher than for the unadjuvanted group.

**Table 5 Post-vaccination HI antibody immune responses to Q-Pan and D-Pan H5N1 (A/Indonesia/5/2005) formulated with and without AS03 at Day 42 and Day 182 (ATP-I), Q-Pan-001**

Treatment Group	N	SCR <sup>1</sup>		% Subj with HI titer $\geq 40$		GMT (95% CI)
		n	%SCR (95% CI)	n	%SPR (95% CI)	
<b>Day 21</b>						
A (Q-unadj)	75	5	6.7 (2.2, 14.9)	5	6.7 (2.2, 14.9)	6.1 (5.2, 7.1)
B (Q-AS03A)	144	60	41.7 (33.5, 50.2)	60	41.7 (33.5, 50.2)	22.5 (17.8, 28.6)
C (Q-AS03B)	146	60	41.1 (33.0, 49.5)	60	41.1 (33.0, 49.5)	19.9 (15.7, 25.3)
D (D-AS03A)	140	64	45.7 (37.3, 54.3)	64	45.7 (37.3, 54.3)	23.5 (18.3, 30.3)
E (D-AS03B)	142	54	38.0 (30.0, 46.5)	54	38.0 (30.0, 46.5)	16.8 (13.5, 20.9)
<b>Day 42</b>						
A (Q-unadj)	75	13	17.3 (9.6, 27.8)	13	17.3 (9.6, 27.8)	10.5 (8.2, 13.5)
B (Q-AS03A)	144	140	97.2 (93, 99.2)	140	97.2 (93, 99.2)	464.7 (383.4, 563.4)
C (Q-AS03B)	146	131	89.7 (83.6, 94.1)	131	89.7 (83.6, 94.1)	320.7 (246.9, 416.6)
D (D-AS03A)	140	135	96.4 (91.9, 98.8)	135	96.4 (91.9, 98.8)	480.3 (390.5, 590.7)
E (D-AS03B)	142	131	92.3 (86.6, 96.1)	131	92.3 (86.6, 96.1)	347.7 (272, 444.5)
<b>Day 182</b>						
A (Q-unadj)	74	2	2.7 (0.3, 9.4)	3	2.7 (0.3, 9.4)	5.6 (5.1, 6.2)
B (Q-AS03A)	141	77	54.6 (46, 63)	77	54.6 (46, 63)	27.8 (22.8, 33.8)
C (Q-AS03B)	145	66	45.5 (37.2, 54)	66	45.5 (37.2, 54)	22.6 (18.4, 27.9)
D (D-AS03A)	138	67	48.6 (40, 57.2)	68	49.3 (40.7, 57.9)	26.1 (20.7, 32.8)
E (D-AS03B)	138	62	44.9 (36.5, 53.6)	63	45.7 (37.2, 54.3)	22.6 (18.3, 28)

N = number of subjects with available results

n = number of responders or subjects with titre within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Source: compiled from the applicant's tables

### Equivalence between Quebec- versus Dresden-manufactured Vaccines –

Table 6 presents the comparison between Quebec- and Dresden-manufactured vaccines, as assessed by GMT. The equivalence criterion was met for both antibodies.

**Table 6 Adjusted GMT ratios for subjects receiving Quebec antigen with full or half strength adjuvant compared with subjects receiving Dresden antigen with full or half strength adjuvant at Day 42, by HI antibody (ATP-I), Q-Pan-001**

Antibody	Quebec N	Quebec Adjusted GMT	Dresden N	Dresden Adjusted GMT	GMT ratio (Q/D)	GMT ratio 95%CI LL	GMT ratio 95%CI UL
A/Indonesia/5/05	290	371.	282	396.	0.94	0.75	1.17
A/Vietnam/1194/04	290	36.	282	31.	1.16	0.92	1.46

Dresden = D-AS03A and D-AS03B      Quebec = Q-AS03A and Q-AS03B

Adjusted GMT = geometric mean antibody titer adjusted for age strata, baseline titer

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMT ratio (Ancova model: adjustment for baseline titer – pooled variance)

### **Immunogenicity Conclusions:**

- Immunogenicity of Q-Pan H5N1 with full-strength or half-strength AS03 adjuvant was markedly superior to Q-Pan H5N1 without adjuvant, as determined by seroconversion rates and GMTs at Day 42.
- All treatment groups receiving adjuvanted vaccine exceeded CBER's requirements for seroconversion rate and proportion of subjects attaining homologous virus HI titers  $\geq 40$  at Day 42.
- Q-Pan H5N1 and D-Pan H5N1, when combined with AS03, were equivalent with regard to HI antibody responses to both A/Indonesia/5/05 and A/Vietnam/1194/04.

### **3.1.6 Safety Results**

Analysis of safety was performed on the Total Vaccinated Cohort (TVC). All 680 subjects were included in the total vaccinated cohort.

The incidence of solicited local and general symptoms was higher among subjects receiving adjuvanted vaccine. Specifically, symptoms such as injection site pain, muscle aches, and fatigue increased with the addition of adjuvant; however, these symptoms were not generally severe. Reducing the adjuvant dose did not markedly alter the overall rate of solicited local and general symptoms, but did, in particular, decrease the rate of grade 3 symptoms. This was especially notable in the case of injection site pain, but the same pattern, although less marked, also could be discerned for other solicited symptoms. The duration of solicited symptoms was not, however, consistently greater in adjuvant recipients, nor was it adjuvant dose-responsive. In addition, reactogenicity did not worsen after the second dose relative to the first. Solicited local and general symptoms are summarized in Table 7.

There were no notable findings among the unsolicited AE, SAE, or vital sign data. The vaccine had a relatively low incidence of unsolicited adverse events in all treatment groups, with no statistically notable difference between adjuvanted and unadjuvanted vaccine. No unsolicited event was reported by more than 5% of subjects overall or more than 10% of subjects in a treatment group. The most commonly reported events were headache, nausea, pharyngolaryngeal pain, nasopharyngitis, and back pain -- none of which showed a clear association with receipt of the adjuvanted vaccine products, or an adjuvant dose response.

No deaths or vaccine-related SAEs were reported during the initial period through Day 42. Four SAEs were reported in 2 subjects (1 each in Group B [Q-AS03<sub>A</sub>] and Group D [D-AS03<sub>A</sub>]). The subject in Group B received diagnoses of cholelithiasis and pancreatitis on Day 13, after receiving one dose of study vaccine. Neither event was considered to be vaccine-related. The subject in Group D received diagnoses of ovarian cyst and uterine leiomyoma 9 days after receiving the second dose of study vaccine. Neither event was considered to be vaccine related.

**Table 7 Incidence of solicited local and general symptoms overall per subject (TVC) Q-Pan-001**

		Group A (Q-unadj) N = 78	Group B (Q-AS03 <sub>A</sub> ) N = 152	Group C (Q-AS03 <sub>B</sub> ) N = 151	Group D (D-AS03 <sub>A</sub> ) N = 151	Group E (D-AS03 <sub>B</sub> ) N = 148
	Type	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Local Symptom</b>						
Pain	All	18 (23.1)	133 (87.5)	130 (86.1)	139 (92.1)	124 (83.8)
Pain	Grade 3	1 (1.3)	9 (5.9)	2 (1.3)	10 (6.6)	3 (2.0)
Redness	All	0	7 (4.6)	2 (1.3)	9 (6.0)	6 (4.1)
Redness	> 100 (Gr. 3)	0	0	0	0	0
Swelling	All	0	12 (7.9)	10 (6.6)	21 (13.9)	9 (6.1)
Swelling	> 100 (Gr. 3)	0	0	0	0	0
<b>General Symptom</b>						
Fatigue	All	16 (20.5)	64 (42.1)	50 (33.1)	67 (44.4)	69 (46.6)
Fatigue	Grade 3	2 (2.6)	6 (3.9)	3 (2.0)	4 (2.6)	2 (1.4)
Headache	All	25 (32.1)	71 (46.7)	61 (40.4)	66 (43.7)	61 (41.2)
Headache	Grade 3	1 (1.3)	10 (6.6)	2 (1.3)	6 (4.0)	4 (2.7)
Joint pain at other location	All	12 (15.4)	49 (32.2)	36 (23.8)	53 (35.1)	39 (26.4)
Joint pain at other location	Grade 3	1 (1.3)	7 (4.6)	2 (1.3)	3 (2.0)	4 (2.7)
Muscle aches	All	15 (19.2)	74 (48.7)	64 (42.4)	86 (57.0)	63 (42.6)
Muscle aches	Grade 3	1 (1.3)	9 (5.9)	4 (2.6)	3 (2.0)	6 (4.1)
Shivering	All	4 (5.1)	18 (11.8)	21 (13.9)	27 (17.9)	17 (11.5)
Shivering	Grade 3	0	5 (3.3)	0	1 (0.7)	3 (2.0)
Sweating	All	6 (7.7)	23 (15.1)	12 (7.9)	24 (15.9)	21 (14.2)
Sweating	Grade 3	0	3 (2.0)	0	3 (2.0)	3 (2.0)
Temperature (°C)	All	0	4 (2.6)	4 (2.6)	12 (7.9)	11 (7.4)
Temperature (°C)	≥ 39	0	0	0	0	1 (0.7)

### 3.1.7 Subgroup Analyses

#### **Immunogenicity –**

**Age:** As expected, the Day 42 antibody levels elicited by Q-Pan-AS03<sub>A</sub> were generally higher for the younger 18-40 years age group and lower for the 41-64 years group (GMT 602.4 vs 334.5), but with similar SCR (96.3% vs 98.4%). In both age subgroups, the adjuvant effect was demonstrated, and the immune responses to Q-Pan H5N1 vaccine with AS03<sub>A</sub> at Day 42 met the CBER criteria.

**Gender:** At full adjuvant dose, Q-Pan H5N1 produced a higher GMT level at Day 42 in females compared to males (611.2 vs 345.1), with similar SCR (100% vs 94.2%) for both genders. The adjuvant effect was demonstrated and the CBER immunogenicity criteria were met for both genders.

**Safety –** No notable differences between the two age subgroups or between the two genders were observed with respect to their safety profile.

### 3.1.8 Conclusions

Adjuvant effect was demonstrated for both full- and half-strength AS03 in combination with Quebec-manufactured A/Indonesia/5/05 in terms of both GMT and SCR enhancement. Q-Pan

H5N1 and D-Pan H5N1 were shown to be immunogenically equivalent based on GMT. A/Indonesia/5/05 antigens from both sources and in combination with either full- or half-strength AS03 fulfilled CBER criteria for accelerated approval based on homologous virus HI titer responses.

Subjects receiving either antigen in combination with AS03 showed substantially increased rates of local reactogenicity, especially injection site pain. Half-strength AS03 demonstrated little reduction in all local pain relative to full-strength, but did notably decrease grade 2 and 3 reports. A similar pattern was seen with most solicited local and systemic symptoms, although this was much less marked for systemic symptoms. The duration of solicited symptoms was not, however, consistently greater in adjuvant recipients, nor was it adjuvant dose-responsive. In addition, reactogenicity did not worsen after the second dose relative to the first.

***Reviewer's Comments:***

*The applicant performed the analyses as planned. Results were verified by the reviewer.*

### **3.2 STUDY Q-PAN 002**

**Study Title:** A Phase III, observer-blind, randomized, placebo-controlled, multi-center trial to evaluate the safety and immunogenicity of a two-dose series of monovalent A/Indonesia/5/05 (H5N1) vaccine antigen in association with AS03 adjuvant in adults aged  $\geq 18$  years.

The study was conducted in 2008 by 40 investigators in 2 countries (US and Canada).

**Objectives:**

*Primary:*

- To demonstrate that Q-Pan H5N1 in association with AS03 elicits an immune response, measured by post-immunization vaccine-homologous virus HI titers at Day 42, which meets or exceeds CBER guidance targets for seroconversion (SCR) and proportions of subjects with titers  $\geq 40$  (SPR). This was to be tested separately for 2 age strata: 18 to 64 years of age and  $> 64$  years of age.

*Criteria for Evaluation:*

(1) The lower limit of the 95% CI for SCR must be  $\geq 40\%$  in subjects 18-64 years of age, and  $\geq 30\%$  in subjects  $>64$  years of age; *and*

(2) The lower limit of the 95% CI for SPR must be  $\geq 70\%$  in subjects 18-64 years of age, and  $\geq 60\%$  in subjects  $>64$  years of age

- To demonstrate lot consistency of 3 consecutive lots of Q-Pan H5N1 combined with 3 consecutive lots of AS03 manufactured in Rixensart, based on vaccine-homologous virus HI GMTs in healthy younger adults 18 to 49 years of age.

*Criteria for Evaluation:*

The 2-sided 95% confidence bounds for all the 3 pairwise GMT ratios should be entirely within the interval 0.67 to 1.5.

- To describe the safety of Q-Pan H5N1 adjuvanted with AS03 in terms of solicited local and general reactogenicity events, unsolicited adverse events (AEs), and serious adverse events (SAEs) in comparison to placebo in adult subjects  $\geq 18$  years of age.

*Secondary:*

- To describe the immunogenicity of the vaccine in terms of vaccine-homologous virus HI titers for 6 months following the first dose of vaccine.
- To further describe the immunogenicity of the vaccine regimen in the 2 age strata in terms of microneutralization titers specific for the vaccine-homologous virus and for one or more drift-variant viruses.

### 3.2.1 Study Design

This was a randomized, observer-blind, multi-centered, placebo-controlled eight-arm trial. Subjects were to be randomized in a 3:1 ratio to treatment with active product, comprising 1 of 3 lots of study vaccine or placebo. Randomization was stratified by age; thus, subjects were over randomized at a 1:1:1:1 ratio to receive 1 of 4 treatments. Within each treatment, the randomization was to target an age interval ratio of 1.5 (18 to 30 years): 1.5 (31 to 49 years): 1 (50 to 64 years): 1.5 (65 to 75 years): 0.5 (> 75 years).

**Table 8 Study Groups, by Age Strata and Study Vaccine Lot, Q-Pan-002**

Study Arms	Age in Years <sup>1</sup>	Antigen lot	Adjuvant lot	Placebo	Subject (N)	Tested for Lot consistency	Tested for SCR/SPR 18-64 yrs	Tested for SCR/SPR >64 yrs
A	18-49	A	1		555	420	1260 (420/lot, arms A,B,C combined)	
B	18-49	B	2		555	420		
C	18-49	C	3		555	420		
D	18-49			PBS	555		60	
E	50-64	A B C	1 2 3		555 (185/lot)		420 (140/lot, combined with arms A, B, & C)	
F	50-64			PBS	185		20	
G	> 64	A B C	1 2 3		1110 (370/lot)			420 (140/lot, combined)
H	> 64			PBS	370			40

Subjects in Groups A-D were to be stratified by age 18-30 years and 31-49 years. Subjects in Groups G & H were to be stratified by age 64-75 years and >75 years.

### Endpoints

#### **Immunogenicity endpoints –**

*Primary*

- HI antibody titer against vaccine-homologous virus at Day 42 (21 days after the second dose of H5N1 vaccine) for younger adults age 18 to 64 years and older adults age > 64 years.

*Secondary*

- HI antibody titer against vaccine-homologous virus at 6 months after the first dose of H5N1 vaccine) for younger adults age 18 to 64 years and older adults age > 64 years.
- Microneutralization titer against vaccine-homologous and drift variant H5N1 virus in subjects receiving 2 doses of study vaccine.

**Safety endpoints –**

- The occurrence of specifically-solicited local and general signs and symptoms during a 7-day follow-up period after each vaccine administration, and overall per subject considering both post-immunization periods.
- The occurrence of all unsolicited adverse events during a 21-day follow-up period for each vaccine administration, as well as overall (Day 0 through Day 84).
- The occurrence of serious adverse events and medically-attended events Day 0 through Day 364.

**3.2.2 Statistical Methods**

**Analysis Populations:** defined similarly as for study Q-Pan 001.

- According to Protocol cohort for immunogenicity analysis (ATP-I)
- According to Protocol cohort for immunogenicity analysis (ATP-S)
- Total Vaccinated cohort (TVC)

**Analysis of Immunogenicity:**

Primary immunogenicity analyses were performed on the ATP-I cohort.

Two-sided 95% confidence intervals (CIs) were calculated for SCR and SPR within each major age stratum for the Q-Pan H5N1 group, i.e., pooled from Study Arms A + B + C + E for 18-64 years of age; and Study Arm G for the > 64 years of age. The SCR and SPR estimates for placebo control subjects 18-64 years of age were calculated from pooled Study Arms D + F; and the placebo group > 64 years of age was Study Arm H.

To assess lot consistency, two-sided 95% CIs were calculated for the GMT ratio to evaluate the equivalence between study arm A vs. B, arm A vs. C, and arm B vs. C in the young adult age group (age 18-49). If the 2-sided 95% confidence bounds for all the GMT ratios are within the interval of 0.67 to 1.5, then lot consistency will be concluded.

**Analysis of Safety:**

Primary safety analyses were performed on the TVC cohort.

The incidence rates and exact 95% CIs were tabulated for each treatment group and for each age stratum for solicited local and general symptoms of any intensity, Grade  $\geq$  2, and Grade 3, medically attended events, and solicited general events with relationship to vaccination that occurred during the solicited follow-up period.

The percentage of subjects with at least one unsolicited AE, and also the percentage of doses followed by at least one unsolicited AE, classified by MedDRA up to 21 days after each H5N1 vaccination and, additionally, up to 84 days post 1<sup>st</sup> dose, was tabulated with exact 95% CI for

each treatment group and age stratum. Serious adverse events and withdrawals due to adverse event(s) were described in detail.

### 3.2.3 Disposition of Subjects

**Table 9 Subject enrollment and disposition, Q-Pan-002**

	Total 18-64 years	Total >64 years	18-64 years Q-Pan	18-64 years Placebo	>64 years Q-Pan	>64 years Placebo
Total enrolled cohort	3072	1489	-	-	-	-
Total vaccinated cohort	3072	1489	2304	768	1118	371
ATP safety cohort	2952	1447	2220	732	1087	360
ATP immunogenicity cohort	1647	436	1571	76	396	40

### 3.2.4 Demographics Characteristics

The demographic information for the TVC cohort was similar to that of the ATP-I cohort. The demographic profile of the 2 treatment groups and 2 age strata were comparable with respect to gender and racial distribution. In both age strata, there were more female subjects in the study than male subjects, and the population was predominantly Caucasian.

### 3.2.5 Immunogenicity Results

**Post-Vaccination Immune Responses** – GMT, Seroconversion rate (SCR) and Proportion of Subjects attaining HI titer  $\geq 40$  (SPR)

As shown in the table below, at Day 42, recipients of Q-Pan H5N1 in both age strata met the CBER criteria for SCR and SPR;

**Table 10 A/Indonesia/5/2005 HI antibody response parameters at Day 42 (21 days post dose 2) and Day 182 (6 months post dose 1), Q-Pan-002**

Treatment Group	Age (yr)	N	n	Seroconversion Rate (95% CI)	Seroprotection Rate (95% CI)	GMT (95% CI)
<b>Day 42</b>						
Q-Pan H5N1	18-64	1571	1427	90.8 (89.3, 92.2)	90.8 (89.3, 92.2)	249.0 (231.8, 267.5)
Saline placebo	18-64	76	1	1.3 (0.0, 7.1)	1.3 (0.0, 7.1)	5.1 (4.9, 5.4)
Q-Pan H5N1	> 64	396	295*	74.0 (69.4, 78.2)	74.5 (69.9, 78.7)	81.9 (69.7, 96.2)
Saline placebo,	> 64	40	1	2.5 (0.1, 13.2)	2.5 (0.1, 13.2)	5.5 (4.5, 6.8)
<b>Day 182</b>						
Q-Pan H5N1	18-64	366	225	61.5 (56.3, 66.5)	61.5 (56.3, 66.5)	36.2 (31.0, 42.2)
Saline placebo	18-64	37	1	2.7 (0.1, 17.8)	2.7 (0.1, 14.2)	5.5 (4.8, 6.5)
Q-Pan H5N1	> 64	91	60**	64.8 (54.1, 74.6)	65.9 (55.3, 75.5)	44.8 (33.3, 60.4)
Saline placebo	> 64	19	0	0.0 (0.0, 17.6)	0.0 (0.0, 17.6)	5.4 (4.6, 6.3)

\*n=293 for SCR; 295 for SPR

\*\*n=59 for SCR; 60 for SPR

**Reviewer’s Comments:**

The immune responses to Q-Pan H5N1 successfully met the CBER immunogenicity criteria for both the adults and the elderly populations. However, it is noted that the post-vaccination GMTs for the 18-64 age group observed in study -002 were substantially lower than the GMTs observed in study -001. The Day 42 GMT (249.0 with 95% CI 231.8 to 267.5) for the Q-Pan H5N1 group in study -002 is almost 2-fold lower than the Day 42 GMT for the Q-Pan H5N1 group in study -001 (464.7 with 95% CI 383.4 to 563.4). It is not known what could have contributed to the observed differences between the two studies, other than their being conducted at different times and in different study populations. Therefore, cross study comparisons may not be prudent.

**Lot Consistency –**

**Table 11 Adjusted ratios of H5N1 GMTs for Q-Pan Lot A v.s. Lot B, Lot A v.s. Lot C, and Lot B v.s. Lot C at Day 42 in subjects 18-49 years of age (ATP-I), Q-Pan-002**

	Lot A N	Lot A GMT	Lot B N	Lot B GMT	Lot C N	Lot C GMT
Adjusted GMT	394	275.8	379	291.7	394	333.5

  

	Adjusted GMT Ratio (95% CI)
Q-Pan Lot A v.s. Lot B	0.95 (0.78, 1.15)
Q-Pan Lot A v.s. Lot C	0.83 (0.68, 1.00)
Q-Pan Lot B v.s. Lot C	0.87 (0.72, 1.06)

Lot A = GSK1557484A Lot A + AS03 Lot 1 (Study arm A)  
Lot B = GSK1557484A Lot B + AS03 Lot 2 (Study arm B)  
Lot C = GSK1557484A Lot C + AS03 Lot 3 (Study arm C)  
Adjusted GMT = geometric mean antibody titer adjusted for baseline titer  
N = Number of subjects with both pre- and post-vaccination results available  
95% CI = 95% confidence interval for the adjusted GMT ratio (Ancova model: adjustment for baseline titer – pooled variance with the 3 lots groups)

As shown in the table above, the lot consistency criterion was met for all 3 pairwise comparisons.

**Immunogenicity Conclusions:**

Both primary immunogenicity objectives (CBER criteria on SPR and SCR, and lot-consistency criteria) were met. Q-Pan H5N1 was immunogenic, based on the SPR and SCR criteria in both adult and elderly populations. Lot consistency was also demonstrated.

**Reviewer’s Comments:**

The applicant performed the analyses as planned. Results were verified by the reviewer.

**3.2.6 Safety Results**

Analysis of safety was performed on the TVC as a whole, and also separately for subjects in the 18 to 64 years and > 64 years age strata. All 4561 subjects (3422 in the Q-Pan group, 1139 in the placebo group), including 3072 subjects in the 18 to 64 years age group (2304 in the Q-Pan group, 768 in the placebo group) and 1489 subjects in the > 64 years age group (1118 in the Q-Pan group, 371 in the placebo group), were included in the TVC.

### **Solicited local and general signs and symptoms Days 0-6:**

The overall per subject incidences of solicited local and general symptoms reported during the 7-day post-vaccination period are summarized in the following table. The incidence was higher among the subjects receiving Q-Pan compared with those receiving placebo, and was lower among the elderly compared with the 18-64 years adults.

**Table 12 Subject incidence of solicited local and General symptoms overall (Total Vaccinated cohort), study Q-Pan-002**

		Overall	Overall	18 – 64 yrs	18 – 64 yrs	> 64 yrs	> 64 yrs
Local Symptom n (%)	Type	Q-Pan H5N1 N = 3376	placebo N = 1122	Q-Pan H5N1 N = 2267	placebo N = 754	Q-Pan H5N1 N = 1109	placebo N = 368
Pain	All	2808 (83.2)	224 (20.0)	2024 (89.3)	171 (22.7)	784 (70.7)	53 (14.4)
	Grade 3	156 (4.6)	8 (0.7)	141 (6.2)	6 (0.8)	15 (1.4)	2 (0.5)
Redness	All	287 (8.5)	8 (0.7)	181 (8.0)	7 (0.9)	106 (9.6)	1 (0.3)
	Grade 3	4 (0.1)	0 (0)	4 (0.2)	0 (0)	0 (0)	0 (0)
Swelling	All	351 (10.4)	8 (0.7)	241 (10.6)	7 (0.9)	110 (9.9)	1 (0.3)
	Grade 3	4 (0.1)	0 (0)	3 (0.1)	0 (0)	1 (0.1)	0 (0)
General symptom, n (%)	Type	Q-Pan H5N1 N = 3375	placebo N = 1123	Q-Pan H5N1 N = 2266	placebo N = 755	Q-Pan H5N1 N = 1109	placebo N = 368
Fatigue	All	1148 (34.0)	253 (22.5)	890 (39.3)	189 (25.0)	258 (23.3)	64 (17.4)
	Grade 3	107 (3.2)	26 (2.3)	89 (3.9)	21 (2.8)	18 (1.6)	5 (1.4)
Headache	All	1179 (34.9)	312 (27.8)	932 (41.1)	249 (33.0)	247 (22.3)	63 (17.1)
	Grade 3	97 (2.9)	27 (2.4)	89 (3.9)	24 (3.2)	8 (0.7)	3 (0.8)
Joint pain at other location	All	853 (25.3)	136 (12.1)	645 (28.5)	97 (12.8)	208 (18.8)	39 (10.6)
	Grade 3	63 (1.9)	10 (0.9)	55 (2.4)	8 (1.1)	8 (0.7)	2 (0.5)
Muscle aches	All	1526 (45.2)	231 (20.6)	1188 (52.4)	175 (23.2)	338 (30.5)	56 (15.2)
	Grade 3	109 (3.2)	21 (1.9)	95 (4.2)	17 (2.3)	14 (1.3)	4 (1.1)
Shivering	All	563 (16.7)	109 (9.7)	456 (20.1)	87 (11.5)	107 (9.6)	22 (6.0)
	Grade 3	66 (2.0)	12 (1.1)	58 (2.6)	9 (1.2)	8 (0.7)	3 (0.8)
Sweating	All	362 (10.7)	82 (7.3)	314 (13.9)	67 (8.9)	48 (4.3)	15 (4.1)
	Grade 3	28 (0.8)	13 (1.2)	26 (1.1)	11 (1.5)	2 (0.2)	2 (0.5)
Temperature ≥38°C	All	156 (4.6)	38 (3.4)	121 (5.3)	32 (4.2)	35 (3.2)	6 (1.6)
	≥39	31 (0.9)	10 (0.9)	28 (1.2)	10 (1.3)	3 (0.3)	0 (0)

N= number of subjects with at least one documented dose  
n/= number/percentage of subjects reporting the symptom at least once.

Among the solicited local symptoms, pain was most commonly reported in both the Q-Pan group and the placebo group (per subject any grade incidence: overall, 83% and 20% respectively; 18-64 years, 90% and 23% respectively; >64 years, 71% and 14% respectively). However, the incidence of Grade 3 pain was relatively low: overall, 5% and 1% in the Q-Pan group and placebo group respectively; 18-64 years, 6% and 1% respectively; >64 years, 1% and 0.5% respectively.

Among the solicited general symptoms, muscle aches were most commonly reported, and at a higher rate for the Q-Pan group than the placebo group (per subject any grade incidence: overall, 45% and 21%, respectively; 18-64 years, 52% and 23%, respectively; >64 years, 31% and 15%, respectively). Similarly, the incidence of Grade 3 muscle aches was relatively low. Headache was the second most commonly reported solicited general symptom overall across treatment groups, and was reported at a modestly higher rate for the Q-Pan group (35%) than the saline placebo group (28%).

#### **Unsolicited AEs Days 0-84.**

Overall, 1484 (43.4%) subjects in the Q-Pan group and 451 (39.6%) subjects in the placebo group reported at least one unsolicited AE. The vaccine had a relatively low incidence of unsolicited AEs in all groups. No unsolicited AE was reported by more than 4.6% of subjects in either treatment group.

The most commonly reported events were non-specific, intercurrent symptoms such as nasopharyngitis, oropharyngeal pain, headache, upper respiratory tract infection, cough, and diarrhea -- none of which showed a clear association with receipt of active vaccine product.

#### **SAEs and MAEs Day 0 through Day 364**

**MAEs.** Considering data through Day 379 (end of the Day 364 window), at least one unsolicited, MAE was reported by 1027 (30%) subjects in the Q-Pan group and 346 (30.4%) subjects in the placebo group. There were no notable imbalances between treatment groups or age strata by system organ class or by preferred term.

**AESIs/pIMDs** (AEs of special interest / potentially immune-mediated disorders). Overall, 14 subjects reported AESIs/pIMDs, including 13 subjects (0.38%) in the Q-Pan group and 1 subject (0.09%) in the placebo group; 8 subjects were 18 to 64 years of age; 5 subjects were > 64 years old.

**SAEs, Deaths, and Withdrawals Due to an AE.** Through Day 364, 11 subjects died, 4 (0.12%) in the Q-Pan group (due to myocardial infarction, metastases to the liver and metastatic ovarian cancer, malignant neoplasm, aggravated diabetes mellitus, and exacerbation of liver disease), and 7 deaths (0.61%) in the placebo group. There were 149 subjects (109 of 3422 in the Q Pan group [3.2%], 40 of 1139 [3.5%] in the placebo group) experienced at least one non-fatal SAE; none were considered by the investigator to be related to study vaccine. Nine subjects (4 Q-Pan subjects [0.1%] and 5 placebo subjects [0.4%]) experienced an SAE that led to premature discontinuation from the study.

### **Reviewer's Comments:**

*Though there appears to be an imbalance in the occurrence of AESIs/pIMDs between the Q-pan and placebo groups, the study is not powered for detecting increased risks of rare events. The estimated relative risk of pIMDs is 4.3 with 95% CI of 0.7 to 56.9, which includes 1.0. No firm conclusion can be drawn regarding the relationship between Q-Pan H5N1 and the risk of pIMDs based on this pivotal study Q-Pan-002.*

*During the review cycle, the medical reviewer identified two AESI/pIMDs in the Day 182 unsolicited AE dataset (WUNSOL) that were not reported in the final Day 364 clinical study report. The applicant explained that the WUNSOL dataset submitted to the original BLA was not the "clean, final" unsolicited AE dataset. The cleaned, final WUNSOL dataset was submitted in amendment 14 on November 6, 2012. This raised concerns for the medical reviewer regarding the changes the applicant made to those AEs included in the Day 182 datasets which were supposed to be cleaned datasets. Based on the Excel file outlining the differences between the Day 182 and Day 364 datasets GSK submitted on March 1, 2013, the changes made after Day 182 could result in minor changes to the summary for solicited symptoms and unsolicited AEs. However, study conclusions remain unchanged. In a teleconference on March 8, 2013, CBER requested detailed listings of differences between the Day 182 datasets and Day 364 datasets. The results reported in this review are based on the cleaned final dataset. Differences between the Day 182 and Day 364 datasets also include additional MN assay results that were available after the Day 182 analysis. However, the primary immunogenicity endpoints are based on HAI assay results only and thus are not impacted.*

### **3.2.7 Subgroup Analyses**

#### **Immunogenicity** –

**Age:** As expected, the Day 42 antibody levels elicited by Q-Pan H5N1 decreased with age (GMT: 357.3, 163.0, and 81.9 for 18-40, 41-64, and >64 years old groups, respectively; SCR: 94.3%, 86.7%, and 74.0%, respectively). The CBER immunogenicity criteria for SCR and SPR were met for all 3 age subgroups.

**Gender:** Q-Pan H5N1 produced similar immune responses at Day 42 for both genders in the 18-64 years adults, while the immune response was higher in females compared to males (GMT: 102.3 vs 60.5; SCR: 78.9% vs 67.9) among the elderly population.

**Race:** The majority of the study subjects were white. The immune responses to Q-Pan H5N1 appeared to be similar between whites and non-whites for the 18-64 years age group, but higher in whites for the elderly population.

**Safety** – The incidences of pain and muscle aches, the most commonly reported solicited local and general symptoms, appeared to decrease with age and were slightly higher in females than in males. No notable differences between whites and non-whites were observed.

### 3.2.8 Conclusions

Q-Pan H5N1 vaccine met CBER criteria for accelerated approval, based on homologous virus HI titer responses at Day 42 in the 18-64 and >65 age strata. Immunogenic equivalency of 3 consecutive lots of Q-Pan H5N1 manufactured in Quebec combined with 3 consecutive lots of AS03 manufactured in Rixensart was also demonstrated. At Day 182, the HI titers in all Q-Pan groups substantially declined from levels seen at Day 42, but remained notably elevated relative to their pre-vaccination titers.

Subjects receiving Q-Pan H5N1 showed increased rates (any severity grade or grade 3) of local reactogenicity, especially injection site pain. Through the 364 days follow-up period, 11 subjects died (4 Q-Pan subjects [0.12%] and 7 placebo subjects [0.61%]) and 149 subjects (109 Q-Pan subjects [3.2%] and 40 placebo subjects [3.5%]) reported at least one non-fatal SAE. None of these SAEs were considered to be treatment-related. Overall, 14 subjects reported adverse events of special interest / potentially immune-mediated disorders (13 subjects [0.38%] in the Q-Pan group and 1 subject [0.09%] in the placebo group; 8 subjects were 18 to 64 years of age, and 1 subject was > 64 years old.)

### 3.3 Van Buynder *Arepanix*<sup>TM</sup> (Q-Pan H1N1) Effectiveness Study

**Study Title:** A test-negative Case-Control Study to Evaluate the Effectiveness of GSK Biologicals' Adjuvanted Monovalent Inactivated H1N1 Influenza Vaccine (*Arepanix*<sup>TM</sup>) in Young Children (6 months to <10 years of age)

The Van Buynder study was carried out by the New Brunswick Department of Public Health in Canada during the 2009 H1N1 pandemic. This surrogate antigen effectiveness data is used by the applicant as the pivotal effectiveness study to support full traditional approval for Q-Pan H5N1.

Principal investigator: Dr. Van Buynder

H1N1 testing lab: Georges Dumont Lab in Moncton, NB

Publication: *In*

~~474~~ *Emerging Infectious Diseases* ~~178~~ *Respiratory Viruses*

After reaching a formal agreement with the investigator and various administrative/leadership levels within the provincial public health system, GSK performed a site visit, reviewed study data and key documents, and performed an independent statistical analysis. GSK was able to replicate the study analysis results, with minor discrepancies which GSK considered neither statistically significant nor biologically relevant. GSK's updated analyses have been incorporated into the submitted clinical study report.

#### **Study Period:**

*Study initiation date:* Oct 16, 2009

*Vaccination clinics start date:* Oct 26, 2009

*Study start date:* Nov 16, 2009 (3 weeks after vaccination campaign commenced, to allow 14 days for the vaccine to have taken effect and time for development of symptoms and submission of the H1N1 RT-PCR lab test)

*Study completion date:* Dec 02, 2009

*Data lock point:* Dec 11, 2009

### **3.3.1 Study Design**

This was a case-control test negative, retrospective, VE observational study. The parents of all children 6 months to <10 years of age in the province of New Brunswick, Canada, who were tested for H1N1 influenza infection during the study period were contacted for a direct telephone interview to collect information on age, gender, hospitalization, indigenous status, prematurity, immunosuppression, coexisting medical conditions, previous seasonal flu vaccination, and recent pandemic vaccination.

#### **Definitions:**

**Case:** Children were classified as case subjects if the respiratory sample was H1N1 positive (laboratory-confirmed by RT-PCR).

**Control:** Children were classified as control subjects if the H1N1 test was negative and the child met a clinical case definition of influenza-like illness (ILI).

#### **Vaccinated:**

- (1) Received *Arepanrix*<sup>TM</sup> at least 14 days prior to the onset of symptoms
- (2) Received *Arepanrix*<sup>TM</sup> at least 10 days prior to the onset of symptoms (partial vaccination)

The diagnosis of an ILI was confirmed using a simple questionnaire. The vaccination status and date of vaccination were confirmed through access to New Brunswick's universal pandemic vaccination registration program, which recorded the personal details of every person vaccinated in New Brunswick.

#### **Objectives:**

**Primary:** To evaluate the effectiveness of adjuvanted monovalent inactivated H1N1 influenza vaccine in young children (6 months to <10 years of age) through the reduction in relative risk of laboratory-confirmed [via reverse transcriptase-polymerase chain reaction (RT-PCR)] influenza illness.

**Secondary:** To evaluate the effectiveness of partial vaccination with adjuvanted monovalent inactivated H1N1 influenza vaccine in young children (6 months to <10 years of age) through the reduction in relative risk of laboratory-confirmed (via RT-PCR) influenza illness.

### 3.3.2 Statistical Methods

Differences in categorical variables were tested by the chi-square test or Fisher’s exact test if any expected cell size was less than five. The vaccine effectiveness (VE) was estimated by 1 minus the odds ratio (OR) of children vaccinated at least 14 days or 10 days prior to onset of symptoms and not vaccinated (or less than 14/10 days) for cases and controls, i.e.,  $VE=1-OR$ . Furthermore, a multivariate logistic regression analysis was used to calculate the odds ratio of vaccination (versus no vaccination) in cases and controls, adjusted by the potential confounding variables of age (<36 months vs.  $\geq 36$  months), First Nation status, receipt of seasonal influenza vaccine, pre-existing medical conditions, gender, and hospitalization.

### 3.3.3 Study Population

**Table 13 Study population in Van Buynder Study**

<b>Study Population</b>	<b>N</b>
<b>Total number of children</b> aged 0 - <10 yr in New Brunswick	<b>~ 73,310</b>
<b>Total tested</b> for H1N1 infection (~ 0.16% of total population)	<b>116</b>
<b>Total not contactable</b>	<b>17</b>
Not Contactable: No phone number	9
Not Contactable: Phone number incorrect/disconnected	6
Not Contactable: No answer	2
<b>Total Contactable</b>	<b>99</b>
<b>Total Excluded for protocol deviation and refusal to participate</b>	<b>8</b>
Excluded: Not ILI (all 4 are controls)	4
Excluded: Refuse to participate	3
Excluded: Immunosuppression	1
<b>Total Included in the analysis</b>	<b>91</b>
Cases	28
Controls	63

During the study period, a total of 116 children in the target age group were tested for H1N1 infection. Of these, 25 subjects were excluded from the analysis because they could not be contacted by phone (17 subjects), or due to non-compliance with study inclusion/exclusion criteria (4 controls failed to meet the ILI qualification and 1 subject had immunosuppressive treatment), or refused to participate (3 subjects.)

### 3.3.4 Demographic Characteristics

The demographic distribution of the study subjects is shown in Table 14 below. A comparison of cases versus controls showed that cases were more likely to have been in the 36-59 month age group ( $p=0.05$ ). The controls had a higher hospitalization rate (33.3%) than the cases (17.9%). Cases and controls appear to be similar with respect to other characteristics.

**Table 14 Summary of demographic characteristics (cohort for analysis of vaccine effectiveness), Van Buynder Study**

Characteristic/Demographic	Subgroup	H1N1+ N	H1N1+ %	H1N1- N	H1N1- %	P-values
Age	6-35 months	9	32.1	28	44.4	0.051
	36-59 months	9	32.1	7	11.1	
	60-119 months	10	35.7	28	44.4	
Gender	Male	14	50	33	52.4	0.834
First Nation/Aboriginal	Yes	4	14.3	5	7.9	0.449§
Hospitalized	Yes	5	17.9	21	33.3	0.131
Pre-existing medical condition	Yes	4	14.3	15	23.8	0.406
Received a dose of H1N1 vaccine pre-diagnosis	< 10 days	6	21.4	8	12.7	
	< 14 days	7	25	13	20.6	
	14 days or more	0	0	24	38.1	
	Vaccinated after onset*	1	3.6	8	12.7	
	No valid immunizations**	21	75	26	41.3	
Received seasonal flu vaccine in 2009	Yes	5	17.9	12	19	0.893

\* Immunization date is after onset date, range of these immunizations was between 3 to 36 days post-diagnosis

\*\* Either no immunizations or invalid immunization (i.e. vaccinated after onset), the number of H1N1 positives with no immunizations was 20, the number of H1N1 negatives with no immunizations was 18.

§ Fisher's exact test

Source: Table 1 in the applicant's clinical study report for FLU Q-PAN H1N1-AS03-049 DB (116528) (Van Buynder)

### 3.3.5 Results: Vaccine Effectiveness (VE)

The overall rate of receipt of any *Arepanrix*<sup>TM</sup> dose in the cohort of VE analysis, including subjects dosed too late to produce effective immunogenicity, was 58.2% (53/91). According to GSK, this rate is similar to the average vaccine coverage during that period in New Brunswick, indicating that physicians likely did not consider vaccination status when ordering an H1N1 diagnostic test for their pediatric patients with ILI during the period of the study. (Note that by the 2<sup>nd</sup> week of vaccination campaign, >60% of children in New Brunswick had been vaccinated.)

Overall, 26% (24/91) of study subjects were vaccinated at least 14 days prior to symptom onset. All these subjects were controls. No case subjects were vaccinated at least 14 days before symptom onset, resulting in a VE of 100%. The proportion of case subjects regarded as vaccinated is 0% versus 38.1% (24/63) in control subjects. VE is statistically significant for subjects overall (100%, CI 79.5–100%), and for subjects 6 months to <5 years of age (100%, CI 44–100%) and 5 to <10 years of age (100%, CI 56.6–100%), considered separately. The small number of subjects marginally prevented a statistically significant vaccine effectiveness estimate to be reached for subjects 6 months to <3 years of age (VE = 100%, CI -25.7 to 100%) but did permit one for subjects 3 to <10 years of age (VE = 100%, CI 75.5–100%).

Estimated VEs for subjects vaccinated at least 14 days prior to disease onset for all study subjects and for different age groupings are presented in Table 15 below.

**Table 15** *Arepanrix™* Vaccine effectiveness (for subjects vaccinated at least 14 days prior to disease presentation) in Van Buynder Study

Age	Vaccination status	*H1N1+	*H1N1-	Point Estimate	Vaccine Effectiveness (VE) 95% CI
Children 6 months to <10 years	Vaccinated	0	24	VE = 100%	79.5–100%
	Not vaccinated	28	39		
	Total	28	63		
Children 6 months to <5 years	Vaccinated	0	10	VE = 100%	44.0–100%
	Not vaccinated	18	25		
	Total	18	35		
Children 5 years to <10 years	Vaccinated	0	14	VE = 100%	56.6–100%
	Not vaccinated	10	14		
	Total	10	28		
Children 6 months to < 3 years	Vaccinated	0	8	VE = 100%	-25.7–100%
	Not vaccinated	9	20		
	Total	9	28		
Children 3 years to <10 years	Vaccinated	0	16	VE = 100%	75.5–100%
	Not vaccinated	19	19		
	Total	19	35		

\* H1N1+ (presence of H1N1 infection) and H1N1- (absence of H1N1 infection) by RT-PCR assay.

\*\* Fisher's exact one-sided test statistic used as an expected cell size <5 present. Other probabilities were computed with the chi-square test.

Source: Table 2 in the applicant's clinical study report for FLU Q-PAN H1N1-AS03-049 DB (116528) (Van Buynder)

The results of a second analysis defining effective vaccination as occurring at least 10 days before symptom onset are presented in Table 16. The results of this second analysis increased the proportion of case subjects regarded as vaccinated to 3.5% of cases (1/28) and that of control subjects regarded as vaccinated to 46% of controls (29/63), and yield a VE of 95.7% (95% CI = 66.0-99.4%).

**Table 16 Arepanrix™ Vaccine effectiveness (for subjects vaccinated at least 10 days prior to disease presentation) in Van Buynder Study**

Age	Vaccination status	*H1N1+	*H1N1-	Point Estimate	Vaccine Effectiveness (VE) 95% CI
Children 6 months to <10 years	Vaccinated	1	29	VE = 95.7%	66.0–99.4%
	Not vaccinated	27	34		
	Total	28	63		
Children 6 months to <5years	Vaccinated	0	13	VE = 100%	62.8–100%
	Not vaccinated	18	22		
	Total	18	35		
Children 5 years to <10 years	Vaccinated	1	16	VE = 91.7%	21.2–99.8%
	Not vaccinated	9	12		
	Total	10	28		
Children 6 months to < 3 years	Vaccinated	0	10	VE = 100%	11.4–100%
	Not vaccinated	9	18		
	Total	9	28		
Children 3 years to <10 years	Vaccinated	1	19	VE = 95.3% **	62.2–99.9%
	Not vaccinated	18	16		
	Total	19	35		

\* H1N1+ (presence of H1N1 infection) and H1N1- (absence of H1N1 infection) by RT-PCR assay.

\*\* This VE was 100% in Table 3 of the applicant’s clinical study report for FLU Q-PAN H1N1-AS03-049 DB (116528) (Van Buynder). It is corrected by the reviewer.

Since the secondary analysis identified one case among the children vaccinated at least 10 days prior to symptom onset, GSK performed a logistic regression for multivariate analysis to estimate the association between VE and other explanatory variables (e.g., age < 36 or ≥ 36 months, First Nation status, receipt of seasonal vaccine, receipt of pandemic vaccine, pre-existing medical conditions, gender, and hospitalization) in this population. The only variable that had a statistically significant effect was H1N1 vaccination, and the adjusted VE is 96.4% (95% CI = 70.7-99.6%), similar to the estimated VE without covariate adjustment.

### 3.3.6 Discrepancies Between GSK’s Re-analysis Results and the Results in the Van Buynder Publication

GSK’s re-analysis identified some minor errors in the original New Brunswick data analysis that resulted in a few discrepancies between the outcomes of the two analyses.

(1) In Table 1, there are 6 and 7 subjects among cases (instead of 7 and 8) who received an H1N1 vaccine dose less than 10 days and 14 days before the diagnosis, respectively; among controls, 8 and 13 subjects (instead of 16 and 21) received vaccine less than 10 days and 14 days before the diagnosis. In the Van Buynder publication, subjects vaccinated after the symptom onset were included in the category of receiving a dose of H1N1 vaccine <10 days (or <14 days) pre-diagnosis. GSK revised Table 1 and added a category of “No valid immunizations.” This change does not impact the analysis results for the vaccine effectiveness estimation.

(2) In the logistic regression analysis for subjects vaccinated at least 10 days prior to disease, two subjects whose ages were inadvertently missing at the time the analysis was performed for publication submission. Data imputation had been performed by then. Subsequent to publication, the missing age data were included in the dataset provided to GSK. GSK analyzed the corrected data and obtained the same conclusion from the logistic regression analysis.

(3) GSK also noted that both the study protocol and the Van Buynder publication described conditional logistic multivariate analysis. However, since the collected data were not matched (case vs. control), GSK considered unconditional logistic multivariate analysis as the appropriate statistical method and, employing that analysis method, confirmed the study conclusion. The New Brunswick MOH agreed with this approach and confirmed that unconditional logistic multivariate analysis had also actually been performed to yield the results presented in the publication.

GSK considered these discrepancies statistically insignificant and biologically irrelevant, with no impact on any of the study conclusions. GSK's outcomes are represented in the clinical study report submitted to this BLA.

***Reviewer's Comments:***

*Although the authors of the Van Buynder publication concluded that the results suggest that Arepanrix<sup>TM</sup> is effective in preventing laboratory confirmed pandemic H1N1 influenza during the 2009/2010 H1N1 pandemic in children 6 months to <10 years of age, there are limitations with regard to using this study as the basis to support traditional approval of Q-Pan H5N1.*

**1)** *The sample size in this study was very small, and no or few vaccine failures were observed (0 case for subjects vaccinated  $\geq 14$  days and 1 case for subjects vaccinated  $\geq 10$  days prior to the onset of symptoms) such that:*

- *the estimation of VE adjusted for potential confounders/covariates is either not possible or does not provide meaningful information;*
- *the confidence intervals for estimated VEs are wide;*
- *the analyses for different age subgroups are also not very meaningful, given so few vaccinated cases overall.*

**2)** *Since this was a case-control study, there are limitations due to the study design:*

- *A retrospective case-control study evaluates association, not causal relationship.*
- *There may be potential biases/confounders that cannot be assessed or adjusted for. Although a test-negative design is used in many flu vaccine observational studies and is considered a better case-control study design in controlling selection bias due to differential healthcare seeking behavior, the design is still prone to biases.*

*For example:*

*Patients who seek medical attention for ILI during the pandemic may represent more severe cases or may exhibit a more cautious behavior because of various unknown reasons, or they may be more likely to be unvaccinated.*

*Physicians may be less likely to order the H1N1 test for patients vaccinated early enough. It was reported that by the 2<sup>nd</sup> week of vaccination campaign, >60% of children in New Brunswick had been vaccinated. The study started 3 weeks after the vaccination campaign commenced to allow 14 days for the vaccine to have taken effect and time for development of symptoms and submission of the H1N1 lab test. Yet, only ~30% of study subjects were vaccinated at least 10 days or 14 days prior to symptom onset (GSK's 58.2% vaccination rate among the study subjects included 9 subjects vaccinated after ILI onset and 14 subjects vaccinated <10 days before ILI onset). Although a lower vaccination rate among study subjects is not necessarily an indication of the physician's consideration of the patient's vaccination status when ordering the H1N1 test (could also be the result of a highly effective vaccine), it is unknown whether those subjects vaccinated early enough but still had H1N1 test done possess certain conditions or characteristics that could reduce their exposure to H1N1 virus and thus are less likely to be cases.*

*Information on the number of days between ILI onset and sample collection, which affects the H1N1 test result, was not collected and thus was not considered in the analysis.*

*The possibility of other unmeasured confounders cannot be ruled out.*

- 3)** *A large percentage of eligible subjects were not included in the analysis. Of 116 subjects tested for H1N1 infection, 25 were excluded from the study. Only 5 of the 25 were excluded for not meeting the inclusion criteria (4 not ILI, 1 immunosuppressed); therefore, 20 (18% of 111 (116 – 5 = 111) potentially eligible subjects were excluded because they could not be contacted (17) or refused to participate (3).*

*The dataset submitted by the applicant contains records for 109 subjects. There are no data available for 7 (116-109=7) subjects. Since the dataset does not contain information on reasons for exclusion, it is not clear how many of those 18 (109-91=18) subjects included in the dataset, but excluded from the analysis, are among the 20 subjects who may have been eligible. It is also not clear whether those 4 controls excluded for not meeting ILI definitions are among the 18 subjects not included in the analysis. Of the 18 excluded subjects whose data are available in the dataset, 10 are cases and 8 are controls (i.e., there are more cases among the excluded subjects, but fewer cases among the included subjects). Nine (9) of the 10 excluded cases have missing vaccination status, while 2 of the 8 excluded controls have missing vaccination status. It seems that those potentially eligible subjects' being not contactable or refusing to participate may not have occurred at random. It is likely that the majority of those eligible subjects not included in the study are cases, with their vaccination status reported as missing in the dataset.*

*The reviewer's sensitivity analysis showed that the estimated VE and its lower limit of the 95% confidence interval could change substantially with different scenarios assumed for the missing vaccination status.*

*Due to the limitations described above, there appears to be a high degree of uncertainty about the estimated VE. As the only pivotal effectiveness study, this very small Van Buynder study may not be adequate to provide a reliable VE estimate to support traditional approval.*

### **3.4 INTEGRATED SUMMARY OF SAFETY**

The applicant performed two Integrated Summary of Safety (ISS) analyses: one analysis based on Q-Pan and D-Pan H5N1 data, and the other analysis based on Q-Pan and D-Pan H5N1 and H1N1 data.

#### **3.4.1 ISS-1: Q-Pan and D-Pan H5N1**

This analysis was conducted in 2009, using the data available at the time of analysis. The focus of this analysis was to compare the H5N1/AS03 vaccines to the controls.

##### **3.4.1.1 Studies included in the analysis**

Q-Pan: -001, -002

D-Pan: -002, -007, -008, -010, -012, -015

The total safety database for primary immunization series consists of 12,917 subjects 18 years and above; of these, 9,873 subjects received H5N1 antigen with adjuvant, 636 subjects received H5N1 antigen in combination with saline diluent and 2,408 subjects have received control (saline placebo or *Fluarix*®, GSK's seasonal influenza vaccine manufactured in Dresden, Germany). The 636 subjects who received unadjuvanted vaccine and 300 subjects who received a booster exposure to adjuvanted H5N1 antigen were not included in this analysis.

##### **3.4.1.2 Methodology**

**Analysis 1** – This analysis was performed on data obtained in the two studies that incorporated concurrent non-H5N1 controls in blinded designs: Q-Pan-002 (placebo control) and H5N1-008/011 (*Fluarix* control). Data from the groups of subjects having received any primary exposure (one or two doses) to H5N1/AS03 vaccine (referred to collectively as the H5N1/AS03 group in ISS) were compared to data from the pooled groups of subjects who received control treatments.

The main objective of this analysis was to obtain more accurate estimations of the incidences of the solicited AEs as well as the more common unsolicited AEs. The AEs collected, the time frames of AE data collection, and the definitions used to assess severity were sufficiently similar to permit pooling of the data across the two studies. A recognized weakness of this analysis, based on the 3:1 treatment allocation in the largest contributing study, is the limited size of the control group relative to the H5N1/AS03 group.

All analyses were performed on the Total vaccinated cohort. Subject incidence rates (with exact 95% confidence intervals [CI]) were calculated by treatment group for solicited local and general

AEs, unsolicited AEs, SAEs, medically-attended AEs, lymphadenopathy, and AEs of special interest/potentially immune-mediated disorders (AESI/pIMDs) by MedDRA preferred terms (PT). Rates were estimated by dividing the number of subjects reporting a given event at least once during the follow-up period by the total number of subjects who received treatment. Exact 95% CI for proportions within a group were calculated assuming independence between the first and second dose.

Relative risk (RR), with exact 95% CIs, in H5N1/AS03 recipients vs. control subjects was estimated using the exact conditional likelihood approach adjusted for study effect. No multiplicity adjustment was made; the assessment of potential increased RR based a 95% CI with a lower limit  $\geq 1$  thus has exaggerated type I error.

**Analysis 2** – This analysis was based on all 8 trials listed above to further enhance the ability to detect any potential rare AEs not identified in Analysis 1, thus focused on unsolicited AEs and AESIs/pIMDs. AEs were analyzed by MedDRA PT. Incidence rate (with exact 95% CI) and relative risk (with exact 95% CI) of H5N1/AS03 combinations vs. controls were calculated by treatment group for each PT.

### **3.4.1.3 Results**

Analysis 1 included a total of 9632 subjects from studies Q-Pan-002 and H5N1-008/, with 7224 subjects in the H5N1/AS03 group and 2408 subjects in the Control group (1269 subjects in the *Fluarix* group and 1139 subjects in the placebo group.)

Analysis 2 included a total of 12,281 subjects, with 9873 subjects in the H5N1/AS03 group. The Control group comprised the same subjects as Analysis 1.

#### **Safety assessment specific to Analysis 1** –

##### **Solicited AEs**

Pain was the most frequently reported solicited AE in both treatment groups, reported by 85.9% of the subjects in the H5N1/AS03 group and 42.5% of the subjects in the Control group. However, grade 3 pain was reported by only 5.3% and 0.7% of the subjects, respectively. The lower limit of the 95% CI of the RR (H5N1/AS03 group over Control group) for all solicited local AEs (any grade) was above 1.0.

The most frequently reported solicited general AEs in both treatment groups were fatigue, headache, and myalgia, reported by 40-50% of the subjects in the H5N1/AS03 group and 20-30% of the subjects in the Control group after any dose. Grade 3 solicited general AEs were reported by less than 4% of the subjects in the H5N1/AS03 group and less than 2% of the subjects in the Control groups. The lower limit of the 95% CI about the RR estimate (H5N1/AS03 group over Control group) for each of the solicited general AEs of any severity was above 1.0.

##### **Lymphadenopathy**

The frequencies of objective lymphadenopathy findings reported at Days 0, 21, 42 showed no clear time trend and did not increase with successive doses, nor was there a difference between the H5N1/AS03 and placebo groups. The incidence of lymphadenopathy was generally low (1.1 to 2.0%) at all time points.

### **Medially Attended AEs (MAEs) and SAEs**

MAEs were reported by 9.2% of the subjects in the H5N1/AS03 group and 8.3% of the subjects in the Control group. A total of 195 SAEs, corresponding to 193 different events (as determined by MedDRA PTs), were reported for 152 subjects over the 6-month follow-up period. This resulted in an incidence rate of 1.6% for the H5N1/AS03 group, 1.3% for the *Fluarix* group and 1.8% for the placebo group, showing no difference between treatment groups.

### **Safety assessments – Analysis 1 and Analysis 2**

#### **Unsolicited AEs**

Analysis 1 identified 7 PTs for which the overall incidence was >0.1% in the total study population and the lower limit of the exact 95% CI of the RR was  $\geq 1.0$ : nausea, injection site pruritus, injection site reaction, injection site warmth, malaise, cystitis, and insomnia.

Analysis 2 identified 6 of the 7 PTs identified in Analysis 1. Cystitis no longer met the pre-defined criteria in Analysis 2, but identified one additional PT, dizziness.

#### **AESI/pIMDs**

AESI/pIMDs were considered for Analysis 1 and Analysis 2. Analysis 2 provides few additional events and, critically, no additional control data.

A total of 15 AESI/pIMD PTs were identified in the Analysis 1 dataset. Among the 7224 subjects in the H5N1/AS03 group, 14 events occurred in 14 subjects, whereas 1 event occurred in 1 of the 2408 subjects in the pooled control groups. Because of the markedly different group sizes, this apparent disparity (RR = 4.67) is not statistically significant ( $p = 0.137$ , Fisher's exact test.) These AESI/pIMDs were clinically heterogeneous, including 10 PTs in 5 Primary System Organ Classes.

Analysis 2 adds 2649 subjects to the H5N1/AS03 group and 2 AESI/pIMDs, both in the H5N1/AS03 group. The estimated RR is 3.90 ( $p=0.223$  by Fisher's exact test.)

### **3.4.2 ISS-2: Q-Pan and D-Pan H5N1 and H1N1**

This ISS-2, conducted in 2011, is intended to extend the data on less common and medically more serious events through the evaluation of all available data from adult recipients of adjuvanted D-Pan and Q-Pan H5N1 and H1N1 vaccines. The primary focus of ISS-2 is the comparison between AS03-adjuvanted monovalent pandemic vaccines versus unadjuvanted controls (including placebo and unadjuvanted TIV or pandemic H5N1 or H1N1 vaccines) for

assessing the effect of the adjuvant AS03 on MAEs, SAEs, and pIMDs. The specific objectives of this ISS are:

- To develop an estimate of the incidence of MAEs and SAEs after the primary vaccination series, based on the maximum sample size attainable in subjects with comparable data.
- To increase the likelihood of detecting rare pIMDs, in order to generate hypotheses as to whether these could represent adjuvanted (pre-)pandemic influenza vaccine-attributable safety findings that merit further examination.

### 3.4.2.1 Studies included in the analysis

This ISS contains data from a total of 28 studies. All adjuvanted monovalent pandemic vaccine trials with a locked safety dataset covering at least six months post first vaccine exposure were included. All studies included at least one adjuvanted formulation and 14 of them were controlled with plain (unadjuvanted) antigen vaccine or placebo.

H5N1 Q-Pan: -001, -002, -005, -009, -010, -011

D-Pan: -002/030, -007, -008/011, -010/021, -012, -015, -030, -038, -041

H1N1 Q-Pan: -001, -002, -016, -019

D-Pan: -007, -008, -017, -018, -020, -021, -022, -024, -033

### 3.4.2.2 Levels of analysis

- Level 1 – H5N1 only
  - Analysis 1a: primary vaccination only, adjuvanted formulations vs control (unadjuvanted mono- or TIV or place), controlled studies only.
  - Analysis 1b: primary vaccination only, adjuvanted formulations vs control excluding vaccinees received a half dose of adjuvant (AS03<sub>B</sub>), controlled studies only.
  - Analysis 2a: primary vaccination only, safety characterization of adjuvanted formulations based on both controlled and uncontrolled trials.
  - Analysis 2b: similar to Analysis 2a after excluding vaccinees who received AS03<sub>B</sub>.
- Level 2 – H5N1 and H1N1 combined
  - Analysis 3a: primary vaccination only, adjuvanted formulations vs control (unadjuvanted mono- or TIV or place), controlled studies only.
  - Analysis 3b: primary vaccination only, adjuvanted formulations vs control excluding vaccinees received AS03<sub>B</sub>, controlled studies only.
  - Analysis 4a: primary vaccination only, safety characterization of adjuvanted formulations based on both controlled and uncontrolled trials.
  - Analysis 4b: similar to Analysis 4a after excluding vaccinees who received AS03<sub>B</sub>.

- Analysis 5: description of any additional identified pIMD cases following booster vaccination of AS03<sub>B</sub>-adjuvanted, AS03<sub>B</sub>-adjuvanted, or control product.
- Level 3 – H1N1 only
  - Analysis 6a: primary vaccination only, adjuvanted formulations vs control (unadjuvanted mono- or TIV or place), controlled studies only.
  - Analysis 6b: primary vaccination only, adjuvanted formulations vs control excluding vaccinees received AS03<sub>B</sub>, controlled studies only.
  - Analysis 7a: primary vaccination only, safety characterization of adjuvanted formulations based on both controlled and uncontrolled trials.
  - Analysis 7b: similar to Analysis 7a after excluding vaccinees who received AS03<sub>B</sub>.

### 3.4.2.3 Statistical methods

#### Analyses 1a, 1b, 3a, 3b, 6a, and 6b

Person-year incidence rates (per 100,000 person-years) were computed for all endpoints associated with MAEs, SAEs, pIMDs, and AESIs, with exact 95% CIs for both adjuvanted vaccine and control groups. The RR of event in adjuvanted vaccine recipients relative to that in control recipients was estimated, with an exact 95% CI using the exact conditional likelihood approach adjusted for study effect. Each RR for which the 95% CI excluded 1.0 was accepted as suggestive of a potential treatment effect without controlling for the risk for false positive signals. Uncertainty associated with composite endpoints was not taken into account. Homogeneity of the common RR was assessed using a two-sided exact Breslow-Day test. Forest plots were generated for each event where the p-value for homogeneity was <0.2.

#### Analyses 2a, 2b, 4a, 4b, 7a, and 7b

The incidence rates (per 100,000 person-years) for the same endpoints as described above for analysis 1a were re-estimated for the adjuvanted vaccine group only with exact 95% CIs by considering all the primary vaccination studies, controlled and uncontrolled.

### 3.4.2.4 Results

The Analysis 1 dataset includes a total of 10,132 adjuvanted H5N1 vaccine recipients (follow up time 7,608 person-years,) with 9,303 subjects (7,210 person-years) who received H5N1+AS03<sub>A</sub>. The control group includes a total of 3,164 subjects (1,969 person-years.)

The Analysis 3 dataset represents the largest dataset of controlled trials in this ISS. It includes 13,325 subjects (10,783 person-years) who received at least one dose of an AS03-adjuvanted H5N1 or H1N1 vaccine. Of these subjects, 12,270 (10,155 person-years) received an AS03<sub>A</sub>-containing formulation. The corresponding control group includes 6,361 subjects (5,161 person-years.) The treatment allocation was unbalanced. The Analysis 1 dataset has a randomization ratio  $\geq 3:1$ , and the Analysis 3 dataset has a ratio of 2.09:1.

The Analysis 2 dataset includes 11,376 subjects who received adjuvanted H5N1 vaccine and among these 10,547 subjects received H5N1+AS03A vaccine. The Analysis 4 dataset includes 16,160 subjects received H5N1/H1N1+AS03 vaccine in controlled and uncontrolled trials, with 15,105 subjects received H5N1+AS03A.

### **Medically-Attended AEs (MAEs)**

Analysis 1 (controlled studies of H5N1 vaccines) –

The RR (adjuvanted vaccine over control) for experiencing any MAE had a 95% CI which included 1.0. Of the large number of individual PTs examined, only cystitis had a large RR (4.86 (95% CI: 1.21-42.55) in H5N1+AS03 recipients and 5.32 (95% CI: 1.32-46.56) in H5N1+AS03A recipients.)

Analysis 3 (controlled studies of H5N1 or H1N1 vaccines) –

The RR for experiencing any MAE had a 95% CI which included 1.0. In H5N1+ AS03 recipients, three PTs had RRs with 95% CI excluding 1.0: diarrhea (RR=2.91 (1.40-6.63)), seasonal allergy (RR=4.94 (1.09-45.80)), and vulvovaginal candidiasis (RR=7.96 (1.09-35.95)). In H5N1+ AS03A recipients, one additional PT (cystitis) had RR significantly greater than 1.0 (RR=1.93, 95% CI: 1.03-3.83). Based on the review of all diarrhea, seasonal allergy, vulvovaginal candidiasis, and cystitis cases, the applicant concluded that a causal relationship between adjuvanted vaccine and the risk of these MAEs is unlikely, due to lack of temporal clustering and biological plausibility.

Analysis 2 and Analysis 4 (controlled and uncontrolled trials) –

In Analysis 2a, of the 11,376 H5N1 +AS03 recipients (followed up for 4,724 person-years) 2,038 subjects reported MAEs, giving an incidence rate of 43,144.7 (95% CI: 41,286.7 – 45,054.4) per 100,000 person-years. In Analysis 4a, of the 16,160 H5N1/H1N1+AS03 recipients (followed up for 8,112 person-years) 3,742 subjects reported MAEs, giving an incidence rate of 46,128.2 (95% CI: 44,659 – 47,627.4) per 100,000 person-years.

### **SAEs**

Analyses 1 and 3 (controlled trials) –

The 95% CI of the RR for experiencing an SAE included 1.0 in both Analyses 1 and 3. Since the test for heterogeneity was significant, the SAE data were examined for each controlled trial. With the exception of study D-PAN-H5N1-002, the 95% CI for the RR in all trials included 1.0. In study D-PAN-H5N1-002, the imbalance indicated by an RR of 13.0 (95% CI: 2.23 – 523.52) was possibly due to two factors: a 4:1 randomization ratio for subjects receiving adjuvanted vaccine versus control test article recipients and the longer follow-up period for adjuvanted vaccine recipients (up to 36 months after the primary course compared with 6 months for controls.)

Analyses 2 and 4 (controlled and uncontrolled trials) –

In Analysis 2a, of the 11,376 H5N1+AS03 recipients (followed up for 8,225 person-years for SAEs) 271 subjects reported at least one SAE, giving an incidence rate of 3,294.7 (95% CI: 2911.3 - 3708.3) per 100,000 person-years. In Analysis 4a, of the 16,160 H5N1/H1N1+AS03

recipients (followed up for 12,939 person-years for SAEs) 507 subjects reported at least one SAE, giving an incidence rate of 3,918.3 (95% CI: 3,582.8 – 4,272.8) per 100,000 person-years.

Fatal SAEs were reported for a total of 37 subjects (25 received AS03-adjuvanted vaccines as a primary vaccination course and 12 received control test article). Considering all controlled and uncontrolled trials, there was no excess of deaths among adjuvanted vaccine recipients based on the observed case ratio of 2:1, which is the same as the overall randomization ratio of 2:1.

### **Potential Immune-Mediated Diseases (pIMDs)**

Analyses 1, 3, 6 (controlled trials) –

In H5N1+AS03 recipients and in H5N1+AS03<sub>A</sub> recipients, respectively, the RR for experiencing a pIMD was 6.85 (95% CI: 1.10 – 283.38) and 6.68 (95% CI: 1.07 – 276.80) with respect to control test article recipients.

In H5N1/H1N1+AS03 recipients and in H5N1/H1N1+AS03<sub>A</sub> recipients, respectively, the RR for experiencing a pIMD was 1.69 (95% CI: 0.81 – 3.81) and 1.81 (95% CI: 0.85 – 4.11) with respect to control test article recipients.

In H1N1+AS03 recipients and in H1N1+AS03<sub>A</sub> recipients, respectively, the RR for experiencing a pIMD was 1.00 (95% CI: 0.37 - 2.68) and 1.13 (95% CI: 0.42 - 3.05) with respect to control test article recipients.

Analyses 2, 4, 7 (controlled and uncontrolled trials) –

In Analysis 2a, of the 11,376 H5N1+AS03 recipients (followed up for 6,083 person-years for pIMDs) 23 subjects reported a pIMD, giving an incidence rate of 378.1(95% CI: 239.7 - 567.3) per 100,000 person-years. In Analysis 4a, of the 16,160 H5N1/H1N1+AS03 recipients (followed up for 10,797 person-years for pIMDs) 38 subjects reported a pIMD, giving an incidence rate of 351.9 (95% CI: 249.1 - 483.1) per 100,000 person-years. In Analysis 7a, of the 4,784 H1N1+AS03 recipients (followed up for 4,714 person-years for pIMDs) 15 subjects reported a pIMD, giving an incidence rate of 318.2 (95% CI: 178.1 - 524.8) per 100,000 person-years.

Increased RR for pIMDs was noted in adjuvanted H5N1 recipients, but not in adjuvanted H1N1 recipients. The applicant carried out an in-depth review of pIMDs which are also AESIs. The H5N1 studies had an overall subject randomization ratio 3:1 and had no pIMD-specific surveillance in place, while the H1N1 studies had a randomization ratio of 1:1 and utilized a specific approach to pIMD surveillance. Based on the considerations of strength of association, specificity, no apparent temporal relationship, and no biologically plausible explanation for the diversity of disease reported, the applicant concluded that no causal association between AS03-adjuvanted H5N1 and H1N1 vaccines and the risk of pIMDs can be established.

### **AEs of Special Interest (AESIs)**

AESIs by Preferred Term (PT) in controlled trials:

Analyses 1, 3 (controlled trials) –

In H5N1+AS03 recipients and in H5N1+AS03<sub>A</sub> recipients, respectively, the RR for experiencing a CHMP-defined AESI was 1.44 (95% CI: 0.98 – 2.19) and 1.47 (95% CI: 0.99 – 2.24) with respect to control test article recipients. Analyses by individual PT also showed no imbalance for any AESIs in recipients of pandemic vaccine or of control test article. Overall, 147 H5N1+AS03 recipients reported CHMP-defined AESIs. The most frequently reported were: convulsion, hypoesthesia, paresthesia, presyncope, syncope, and urticaria.

In H5N1/H1N1+AS03 recipients and in H5N1/H1N1+AS03 recipients, respectively, the RR for experiencing a CHMP-defined AESI was 1.22 (95% CI: 0.94 – 1.61) and 1.22 (95% CI: 0.93 – 1.60) with respect to control test article recipients. Analyses performed by individual PT also suggested no increased risk for any individual event in adjuvanted vaccine recipients.

#### AESIs identified by narrow SMQ in controlled trials:

For adjuvanted H5N1 vaccine recipients, the RR for experiencing any AESI identified by narrow SMQ was 2.67 (95% CI: 1.21-6.97). The RR for H5N1+AS03<sub>A</sub> recipients was 2.67 (95% CI: 1.20-6.97). There was no imbalance of AESIs as an aggregate in the full set of controlled trials of adjuvanted H5N1/H1N1 vaccines and in adjuvanted H1N1 vaccine recipients. There was overlap in definitions of AESIs and pIMDs. For AESIs not overlapped with pIMDs, no imbalance was detected for any individual events.

It is noted that the 95% CI for the RRs for experiencing any AESI identified by narrow SMQ in adjuvanted H5N1 vaccine recipients (analysis 1) exclude 1.0. However, study heterogeneity in the estimation of the RR for AESIs as an aggregate in each dataset (in analyses 1 and 3) was generally significant at  $p < 0.05$ , suggesting that using a single estimated RR to summarize the risk across all studies may not be appropriate. In studies where a value of RR could be calculated (i.e., there is at least 1 case in the control group), the 95% CIs around the estimated RRs all include 1.0.

#### ***Reviewer's Comments:***

*No imbalance was observed for CHMP-defined AESI identified by PTs in both adjuvanted H5N1 and H5N1+H1N1 recipients. For AESIs identified as an aggregate by narrow SMQ, an increase of risk was found for adjuvanted H5N1 recipients, but not for adjuvanted H1N1 recipients. The applicant believes that the detection of a greater number of AESIs in H5N1+AS03 recipients resulting from the imbalance between H5N1+AS03 and control recipients (randomization ratio is 3:1) led to an overestimation of the RR in H5N1+AS03 recipients (analysis 1 dataset). The numbers of subjects receiving adjuvanted vaccine or control test article in the H1N1 studies were less disparate, and thus no increased RR was observed. In view of the observed significant heterogeneity in the estimation of the RR across studies (which may be partially the result of the small number of subjects receiving control test article in each study, and thus leading to a very unstable estimate of incidence rate for the control group), the statistical reviewer considers an overestimation of the RR in H5N1+AS03 recipients to be likely. The smaller number of control subjects in H5N1 studies is indeed a critical limitation for the evaluation of relative risk of rare events. Given that the heterogeneity in RR estimation across studies is significant and none of the*

95% CIs for the RRs in each individual study exclude 1.0, the relationship between AS03-adjuvanted pandemic vaccines and the risk of AESIs is uncertain.

Analyses 2, 4 (controlled and uncontrolled trials) –

In Analysis 2a, of the 11,376 H5N1+AS03 recipients (followed up for 6,083 person-years) 165 subjects experienced an AESI, giving an incidence rate of 2,712.4 (95% CI: 2,314.3 – 3,159.3) per 100,000 person-years. In Analysis 4a, of the 16,160 H5N1/H1N1+AS03 recipients (followed up for 10,797 person-years) 245 subjects experienced a CHMP-defined AESI, giving an incidence rate of 2269.1 (95% CI: 1993.9 - 2571.8) per 100,000 person-years.

### 3.4.3 ISS Conclusions

- Local and systemic short-term reactogenicity significantly increased in H5N1/AS03 recipients. The most frequently reported solicited AE was injection site pain. The most frequently reported general AEs were fatigue, headache, and myalgia.
- There was no apparent increase in incidence of either MAEs or SAEs among H5N1/AS03 recipients, or among adjuvanted H5N1 and H1N1 recipients.
- The RR for pIMDs in H5N1 studies was 6.85 (95%CI: 1.10-283.38). The lower confidence limit excluded 1.0. However, no increase in RR for pIMDs in H1N1 studies was found.
- No imbalance of AESIs as an aggregate between the adjuvanted and the unadjuvanted arms was identified in the full set of controlled H5N1 and H1N1 studies. For AESIs for which there was no overlap with pIMDs, no imbalance was detected for any individual events.

#### **Reviewer's Comments:**

- *These meta-analyses have many limitations which should be kept in mind when interpreting the results, especially of ISS-2. In order to maximize the number of subjects in the adjuvanted vaccine group, studies were pooled together regardless of site of manufacture, antigen dose, or adjuvant dose. The control group in the analyses of H5N1 and H1N1 studies combined, which focus primarily on assessing the association between the AS03 adjuvant and the pIMDs, included heterogeneous subjects who received placebo alone or unadjuvanted antigens. The studies may have been heterogeneous with respect to study design and conduct too. There is also heterogeneity of data collection, particularly with regard to pIMDs. The list of pIMDs was heterogeneous before a CBER-agreed pIMD list was developed, and thus better, more consistent pIMDs ascertainment is expected in more recent trials. A majority of H5N1 studies were carried out during the period of less intensive pIMD ascertainment, whereas essentially all H1N1 studies were carried out during the period of better ascertainment. Therefore, the comparative results could be confounded by many factors. In addition, multiplicity was not adjusted for the large number of comparisons performed. The false positive rate can be very high. Nevertheless, the analysis results, though not to be used to confirm any long term pIMD signals, can provide useful information for future surveillance.*
- *The pIMDs of special interest are rare events. The complexity in diagnosis for some autoimmune diseases further adds uncertainty to the estimated event rates. With the pre-*

*licensure safety database, even after pooling studies of vaccines manufactured at different sites and of different antigens, it is still not sufficient to assess the likelihood of a causal relationship between adjuvanted pandemic influenza vaccine and the pIMDs.*

- *For more safety evaluation, please refer to the clinical reviewer's review.*

#### **4. COMMENTS TO CBER REVIEW COMMITTEE**

- *The post-vaccination GMTs for the 18-64 age group observed in study -002 are substantially lower than the GMTs observed in study -001. The study populations of the two studies appear to have similar demographic profiles. It is not known what could have contributed to the observed differences between the two studies, that were conducted at different times and had different study populations. Whether the HI assay could be a reason for the observed differences cannot be determined. However, since the immune response levels achieved in both studies are well above the success criteria, the study conclusions are not likely to be affected by potential assay performance issues.*
- *Although the authors of the Van Buynder Q-Pan H1N1 effectiveness study concluded that Arepanrix<sup>TM</sup> is effective in preventing the swine H1N1 influenza, this case-control study has too many limitations to be used as the only pivotal confirmatory effectiveness study to support traditional approval of Q-Pan H5N1.*

#### **5. SUMMARY AND CONCLUSIONS**

**Immunogenicity:** Based on studies Q-Pan-001 and Q-Pan-002, the Q-Pan H5N1 vaccine with AS03 adjuvant appears to be immunogenic. The criteria of SCR (lower bound of 95% CI  $\geq$  40% for 18-64 years and  $\geq$  30% for >64 years) and SPR (lower bound of 95% CI  $\geq$  70% for 18-64 years and  $\geq$  60% for >64 years) were well met. The benefit of the adjuvant AS03 was demonstrated in study Q-Pan-001, and clinical lot consistency was demonstrated in study Q-Pan-002.

**Effectiveness:** Although the results of the Van Buynder study may suggest that the Q-Pan H1N1 vaccine, *Arepanrix*, was effective in preventing H1N1 influenza during the 2009/2010 H1N1 pandemic in children 6 months to <10 years of age, as the only pivotal effectiveness study, this small, retrospective, case-control observational study has too many limitations to provide a reliable VE estimate to support traditional approval of Q-Pan-005.

**Safety:** The AS03 adjuvanted Q-Pan H5N1 vaccine appeared to have increased local and general reactogenicity compared to placebo or H5N1 antigen alone, particularly local injection site pain. No notable imbalance was found for MAEs, SAEs, and AESIs which are not pIMDs. The ISS results showed an increased RR for pIMDs in adjuvanted H5N1 recipients, but not in adjuvanted H1N1 recipients. However, ISS results should be interpreted with caution due to many limitations in such a pooled analysis

Considering the immunogenicity demonstrated and the antigen-sparing advantage highly desired in a pandemic situation, the clinical benefit of Q-Pan H5N1 for pandemic use or for adults at

increased risk of exposure to H5N1 virus appears to outweigh the risk of increased reactogenicity and potential increase of pIMDs incidence. However, due to the differences between the Day 182 and Day 364 safety datasets of study Q-Pan-002 identified by the clinical reviewer, the review team decided that submission of the complete study data package for FLU Q-Pan-002 was warranted in order to make an appropriate regulatory decision.