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Summary Basis of Regulatory Action

Date: January 18, 2019
From: Goutam Sen, Ph.D., Chair of the Review Committee
BLA/ STN#: 103914/6208

Applicant Name: Sanofi Pasteur Inc.

Date of Submission: March 30, 2018
PDUFA Goal Date: January 28, 2019

Proprietary Name: Fluzone® Quadrivalent
Established Name: Influenza Vaccine

Indication: Fluzone Quadrivalent is a vaccine for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine for use in persons 6 month of age and older.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority Doran Fink, M.D., Ph.D, Deputy Director, Clinical, DVRPA

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

The table below indicates the material reviewed when developing the SBRA.

Document title	Reviewer name, Document date
Clinical Review	Susan Wollersheim, M.D., 12/17/2018
Statistical Review	Sang Ahnn, Ph.D., 12/20/2018
Bioresearch Monitoring Review	Haecin Chun, 12/11/2018
APLB Reviewer	Sonny Saini, 10/30/2018
Product Reviewer	Jackeline Soto, M.S., 12/10/2018
Statistical Reviewer of non-clinical data	Jennifer Kirk, Ph.D., 01/02/2019
DMPQ Reviewer	CDR Donald Ertel, M.S., 01/03/2019
Pharmacovigilance Review	Jane Woo, M.D., 12/10/2018

Cross referenced applications:

- IND 14078, Influenza Virus Quadrivalent (A(H1N1)/A(H3N2)/B(Yamagata)/B(Victoria); split virus; chicken eggs) Vaccine, Inactivated
- BLA 103914/5574, To include a quadrivalent influenza virus vaccine formulation (Fluzone Quadrivalent) for the prevention of influenza disease in persons 6 months of age or older caused by influenza viruses contained in the vaccine.

1. Introduction

Fluzone® Quadrivalent (referred as Fluzone-QIV throughout this document) is a split virion, quadrivalent seasonal influenza vaccine (QIV), containing the purified outer membrane protein hemagglutinin (HA) from each of 4 influenza virus strains recommended annually by the World Health Organization (WHO) and the Vaccines and Related Biological Products Advisory Committee (VRBPAC). The Fluzone-QIV HA antigens are derived from viruses propagated in embryonated chicken eggs and are presented as a suspension for injection in prefilled single dose syringes as 0.25-mL and 0.5-mL dose (without thimerosal), as well as a 5-mL multi-dose vial (with thimerosal). Fluzone-QIV is approved for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine for use in persons 6 months of age and older.

Sanofi Pasteur Inc. (SP) submitted this supplemental Biologics Licensing Application (sBLA) on March 30, 2018. With this supplement, SP is seeking approval for use of the 0.5-mL dose of Fluzone-QIV in all persons 6 months of age and older and for modifying the Prescribing Information (PI) accordingly, based on safety and immunogenicity data from a Phase IV clinical study, GRC88. This study evaluates the safety and immunogenicity of two different dose levels of Fluzone-QIV (0.25-mL and 0.5-mL) in healthy children 6 to < 36 months of age. Revised labeling for Fluzone-QIV was also provided with this supplement.

2. Background

Influenza is an acute, highly contagious, respiratory disease condition caused by influenza viruses, mainly spread through respiratory droplets. The illness is accompanied by fever and variable degrees of other systemic symptoms, ranging from mild fatigue to respiratory failure and even death. In the United States (U.S.), an estimated 200,000 children under 5 years of age are hospitalized each year due to influenza complications¹. The highest risk of complications occur among young children and in particular children younger than 2 years, adults 65 years of age or older, pregnant women, and people of any age with underlying chronic conditions that put them at risk for influenza disease. The highest influenza burden in terms of pediatric respiratory disease related hospitalization is seen in infants 6 to 11 months of age², and rates of illness in children younger than 2 years of age are substantially higher than those in children 2 years of age or older^{3,4}.

The Fluzone-QIV formulation was first approved on June 7, 2013, under STN 103914/5574 for use in persons 6 months of age and older. The single dose volume for children 6 to < 36 months of age is 0.25-mL containing 7.5 µg HA of each influenza viral strain, and for persons 3 years of age and older a 0.5-mL dose volume containing 15 µg HA per strain is indicated. Fluzone-QIV (without thimerosal as preservative) is currently licensed in 27 countries. Fluzone-QIV (containing thimerosal as preservative) is currently licensed in 3 countries (U.S., Canada and Mexico). Since product launch, approximately 2 million doses of both Fluzone-QIV formulations combined have been distributed.

The preference for a 0.25-mL dose of influenza vaccine for children 6 through 35 months of age is based primarily on results of large multicenter trials of monovalent and bivalent whole-

virus influenza vaccines conducted in children during the 1970s. These studies demonstrated that adverse reactions were observed in children who were administered whole-virus vaccines, and downward adjustment of the dosage resulted in improved tolerability. However, the introduction of split-virus and subvirion influenza vaccines, which are less reactogenic than whole-virus vaccines, may have eliminated the necessity for dosage adjustments in this young age group. Vaccine efficacy and effectiveness studies have generally demonstrated that inactivated influenza vaccines (IIVs) reduce influenza disease in children, but in some studies the effectiveness in children 6 through 35 months has been lower than that in children 3 years and older. Data from recent studies using Fluarix[®] Quadrivalent and FluLaval[®] Quadrivalent (STN 125127/834 and STN 125163/405) influenza vaccines support the safety of full-dose IIV (15 µg HA per strain; 0.5-mL dose) in this population. Furthermore, data from these studies suggest that in children 6 through 35 months of age, full-dose IIV induces generally higher antibody responses compared to those induced by half-dose vaccine, without causing higher rates of systemic or injection site reactions. In most studies, differences in antibody responses between the full- and half-dose groups were greatest in the youngest age cohorts (i.e., 6 through 11 month-old or 6 through 23 month-old children).

The goal of the GRC88 clinical study was to describe the safety and immunogenicity of the 0.5-mL dose (15 µg HA per strain) as compared to the 0.25-mL dose (7.5 µg HA per strain) of Fluzone-QIV in children 6 through 35 months of age, with the intent to revise the product PI (Dosage and Administration) to include the 0.5-mL dose of Fluzone-QIV as indicated for ages 6 months and older, administered as a 1 or 2 dose regimen as recommended by the U.S. Advisory Committee on Immunization Practices (ACIP).

The GRC88 clinical study protocol titled "Safety and Immunogenicity of Fluzone Quadrivalent Vaccine Administered to Healthy Children 6 Months to < 36 Months of Age" was initially submitted under IND 14078 on February 09, 2015. After several communications between CBER and SP, the protocol was finalized to incorporate CBER's recommendations for assessing safety and immunogenicity by including hypothesis driven outcomes rather than descriptive outcomes. SP revised the study's primary endpoint to assess safety by measuring fever rates and the sample size was increased to adequately power the study to demonstrate non-inferiority of fever rates. In addition, immunogenicity was assessed by measuring geometric mean titer (GMT) ratios and seroconversion (SC) rates with pre-specified non-inferiority success criteria as secondary endpoints.

In this submission, SP is seeking approval for use of the 0.5-mL dose of Fluzone-QIV in all persons 6 months of age and older and modifying the PI accordingly. The study demonstrated that a 0.5-mL dose of Fluzone-QIV has safety and immunogenicity profiles similar to those observed following administration of a 0.25-mL dose of Fluzone-QIV. Based on the results of study GRC88 which demonstrate that the fever rate in 0.5-mL dose group of Fluzone-QIV is not statistically significantly higher than the fever rate in 0.25-mL dose group of Fluzone-QIV and that a 0.5-mL dose of Fluzone-QIV is non-inferior to a 0.25-mL dose of Fluzone-QIV in terms of immunogenicity. SP proposes to offer both dose options for use in children 6 months to < 36 months of age.

3. Chemistry Manufacturing and Controls (CMC)

No manufacturing or facilities- and equipment-related information/data was provided in the supplement as the manufacturing process for making the vaccine remains unchanged.

Environmental assessment

The BLA supplement included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31 c. The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology studies were needed and no such study reports were included in this supplement.

5. Clinical Pharmacology

No new clinical pharmacology information was needed or provided in this supplement.

6. Clinical/ Statistical/Pharmacovigilance

- a) Study GRC88 was a phase IV, observer-blind, randomized, multi-center study to evaluate the safety and immunogenicity of 2 different dose levels of Fluzone-QIV in healthy children 6 to < 36 months of age, administered intramuscularly. Subjects were randomized 1:1 to receive either 0.25-mL of Fluzone-QIV or 0.5-mL of Fluzone-QIV. Enrollment was stratified by age at each site so that approximately 50% of subjects were 6 to <24 months of age and approximately 50% were 24 to <36 months of age. The study was conducted at 38 sites in the U.S. during 2016-2017 influenza season using 2016-2017 season's Fluzone-QIV formulation. Subjects received 1 intramuscular dose of Fluzone-QIV (0.25-mL [Group 1] or 0.5-mL [Group 2]) during Visit 1. Subjects for whom 2 doses of influenza vaccine were recommended per ACIP guidance received a second dose of Fluzone-QIV during Visit 2 (same 0.25-mL or 0.5-mL dose as administered at Visit 1 administered 28 days after Visit 1 with a window of 28–35 days). The study duration was 56-91 days, depending on number of vaccine doses administered.

The primary objective of this study was to compare the rate of any fever (temperature \geq 100.4°F [38.0°C]) following the 0.5-mL dose(s) of Fluzone-QIV vaccine (Group 2) to that following the 0.25-mL dose(s) of Fluzone-QIV vaccine (Group 1) during the 7 days after either vaccination (Dose 1 and Dose 2 combined) in subjects 6 to < 36 months of age. Non-inferiority was demonstrated if the upper bound of the 2-sided 95% CI of the rate difference between Group 2 and Group 1 was < 5%. There were no primary objectives for immunogenicity. The secondary objective of this study was to compare antibody responses induced by the 0.5-mL dose vaccine to those induced by

the 0.25-mL dose vaccine as assessed by the ratio of GMTs and SC rate differences after the final vaccination in subjects 6 to < 36 months of age. Non-inferiority criteria were: (i) the lower bound of the 2-sided 95% CI of the GMT ratio ($\text{GMT}_{0.5\text{-mL}} / \text{GMT}_{0.25\text{-mL}}$) being > 0.67 for each of the 4 virus strains, and (ii) the lower bound of the 2-sided 95% CI of the difference in SC rates ($\text{SC rate}_{0.5\text{mL}} - \text{SC rate}_{0.25\text{mL}}$) being $> -10\%$ for each of the 4 virus strains.

A total of 1950 subjects were randomized into the study: 955 (49.0%) subjects were assigned to receive the 0.25-mL dose of Fluzone-QIV (Group 1) and 995 (51.0%) subjects were assigned to receive the 0.5-mL dose of Fluzone-QIV (Group 2). Six (0.6%) subjects in Group 1 and 3 (0.3%) subjects in Group 2 were randomized but did not receive any vaccine. Of the 1950 randomized subjects, 1460 (74.9%) were randomized to the immunogenicity subset: 715 (74.9%) subjects in Group 1 and 745 (74.9%) subjects in Group 2. A total of 1941 (99.5%) randomized subjects (949 [99.4%] subjects in Group 1 and 992 [99.7%] subjects in Group 2) were included in the Safety Analysis Set. Among the Group 1 and Group 2 subjects, 46.3% and 47.7% of subjects, respectively, received 1 dose of vaccine, and 53.1% and 52.0% of subjects, respectively, received 2 doses of vaccine.

The demographic characteristics were similar between the two treatment groups. Overall, males and females were similarly distributed between and within the 2 vaccine groups (Group 1, 480 [50.6%] males and 469 [49.4%] females; Group 2, 497 [50.1%] males and 495 [49.9%] females). The mean ages of subjects in the 2 vaccine groups were similar (Group 1, 20.4 months; Group 2, 20.5 months). The majority of subjects were white (Group 1, 717 [75.6%] subjects; Group 2, 725 [73.1%] subjects) and non-Hispanic or non-Latino (Group 1, 731 [77.0%] subjects; Group 2, 763 [76.9%] subjects).

Table 1. Clinical Study included in the supplement for Fluzone-QIV

Study Number; Population; Country; Start/End Dates	Study Description	Primary Objective	Test Products; Dosage regimen	Number of Subjects
GRC88 Healthy children 6 to < 36 months of age United States 23 Sept 2016/ 6 March 2017	Phase 4, randomized, observer-blind, 2 arm, multi-center study	To compare the rate of any fever (temperature $\geq 100.4^{\circ}\text{F}$ [38.0°C]) following the 0.5-mL dose of Fluzone QIV to that following the 0.25-mL dose of Fluzone QIV during the 7 days after either vaccination (Dose 1 and Dose 2 combined)	<u>Visit 1:</u> 1 dose of Fluzone QIV Group 1: 0.25 mL Group 2: 0.5 mL <u>Visit 2^a:</u> 1 dose of Fluzone QIV Group 1: 0.25 mL Group 2: 0.5 mL	<u>Total Randomized:</u> Group 1: 955 Group 2: 995 <u>Safety Analysis Set:</u> Group 1: 949 Group 2: 992 <u>PP Analysis Set:</u> Group 1: 502 Group 2: 525

Source: Adapted from STN 103914/6208: module 2.5 Clinical Overview

^a For subjects requiring 2 doses of influenza vaccine, as per Advisory Committee on Immunization Practices guidance, a second dose of the assigned vaccine dose was administered at Visit 2 (28 [window, 28–35] days after Visit 1).

For Dose 1 and Dose 2 combined, the fever rate of Group 2 (12.15%) was not statistically significantly higher than the fever rate of Group 1 (11.31%) based on the pre-specified criterion for non-inferiority, with a difference in fever rates of 0.84% (95% CI: -2.13%; 3.80%).

Table 2. Non-Inferiority Comparison of 2 Dose Levels of Fluzone-QIV (0.5-mL vs 0.25-mL) as Assessed by the Difference in Fever Rates^a – Safety Analysis Set

Group 1 (0.25-mL dose) (N=949)	Group 2 (0.5-mL dose) (N=992)	Group 2 – Group 1
Fever Rate (n/M)	Fever Rate (n/M)	Difference in Fever Rates (95% CI)
11.31% (101/893)	12.15% (113/930)	0.84% (-2.1%; 3.8%)

a: Rate of any fever (temperature ≥ 100.4 F [38.0°C]) during the 7 days after either vaccination (Dose 1 and Dose 2 combined)

N: number of subjects analyzed according to the Safety Analysis Set (subjects who received at least one dose of vaccines)

n: number of subjects experienced fever during 7 days after vaccination

M: number of subjects having valid temperature data during 7 days of vaccination

Source: Reproduced from 5.3.5.1, GRC88 CSR, Section 9, Table 9.24 (STN 103914/6208.0)

Four study sites of the GRC88 clinical study were found to have issues either with safety data integrity [site 009 (n=31)] or with vaccine storage equipment temperature excursion [sites 016 (n=59), 019 (n=26), and 021 (n=7)]. Comparison of fever rates excluding subjects from these four sites also demonstrated that the fever rate of Group 2 was not statistically significantly higher than the fever rate of Group 1 as shown in Table 3.

Table 3. Non-Inferiority Comparison of 2 Dose Levels of Fluzone-QIV (0.5-mL vs 0.25-mL) as Assessed by the Difference in Fever Rates^a – Safety Analysis Set

Group 1 (0.25-mL dose) (N=886)	Group 2 (0.5-mL dose) (N=932)	Group 2 – Group 1
Fever Rate (n/M)	Fever Rate (n/M)	Difference in Fever Rates (95% CI)
11.82% (99/837)	12.58% (110/874)	0.76% (-2.4%, 3.9%)

a: Rate of any fever (temperature ≥ 100.4 F [38.0°C]) during the 7 days after either vaccination (Dose 1 and Dose 2 combined). Excluding subjects from sites 016, 019 and 021 who received vaccine with a potential temperature excursion and subjects from site 009

N: number of subjects analyzed according to the Safety Analysis Set (Excluding subjects from sites 009, 016, 019 and 021)

n: number of subjects experienced fever during 7 days after vaccination

M: number of subjects having valid temperature data during 7 days of vaccination

Source: Static reviewer’s review memo.

Table 4 presents the comparison of the post-final vaccination GMTs between Group 1 (0.25-mL dose) and Group 2 (0.5-mL dose) for subjects in the Per-Protocol Analysis Set. Non-inferior immunogenicity of 0.5-mL dose compared to 0.25-mL dose was demonstrated according to the pre-specified non-inferiority criterion of the lower bound of the 2-sided 95% CI of the GMT ratio ($\text{GMT}_{0.5\text{mL}} / \text{GMT}_{0.25\text{mL}}$) being > 0.67 for each of the 4 virus strains.

Table 4. Non-Inferiority Comparison of 2 Dose Levels of Fluzone-QIV as Assessed by the GMTs^a Ratio – Per Protocol Set.

Antigen Strain	Group 1 (0.25-mL dose) (N=502)		Group 2 (0.5-mL dose) (N=525)		Group 2 / Group 1
	M	GMT	M	GMT	Ratio of GMTs (95% CI)
H1N1	497	219	521	312	1.42 (1.16, 1.74)
H3N2	502	222	524	329	1.48 (1.21, 1.82)
B Victoria	497	262	521	348	1.33 (1.09, 1.62)
B Yamagata	501	247	525	349	1.41 (1.17, 1.70)

a: Post-final vaccination GMTs (28-35 days after the final vaccination). Excluding subjects from sites 016, 019 and 021 who received vaccine with a potential temperature excursion

N: Based on Per-protocol Analysis set

M: number of subjects with available data for the considered endpoint

Source: Adapted from the Table 9.5 in the CSR of GRC88 (STN 103914/6208.5005)

Table 5 presents the comparison of SC rates between Group 1 (0.25-mL dose) and Group 2 (0.5-mL dose) for subjects in the Per-Protocol Analysis Set. Non-inferior immunogenicity of 0.5-mL dose compared to 0.25-mL dose was demonstrated according to the pre-specified non-inferiority criterion of the lower bound of the 2-sided 95% CI of the difference in SC rates ($\text{SC rate}_{0.5\text{mL}} - \text{SC rate}_{0.25\text{mL}}$) being $> -10\%$ for each of the 4 virus strains.

Table 5. Non-Inferiority Comparison of 2 Dose Levels of Fluzone-QIV as Assessed by Difference in SC^a – Per Protocol Set.

Antigen Strain	Group 1 (0.25-mL dose) (N=502)		Group 2 (0.5-mL dose) (N=525)		Group 2 - Group 1
	M	SC rate %	M	SC rate %	Difference in SC rates (95% CI)
H1N1	450	79.3	467	83.9	4.6 (-0.4, 9.7)
H3N2	455	81.5	471	86.6	5.1 (0.4, 9.8)
B Victoria	450	87.3	467	88.7	1.3 (-2.9, 5.6)
B Yamagata	454	88.5	472	91.1	2.6 (-1.4, 6.5)

a: SC (seroconversion) is defined as either a pre-vaccination hemagglutination inhibition titer < 1:10 and a post vaccination titer >= 1:40 or a pre-vaccination titer >= 1:10 and at least a 4-fold increase in post-vaccination titer (considered separately for each strain). Excluding subjects from sites 016, 019 and 021 who received vaccine with a potential temperature excursion

N: Based on Per-protocol Analysis set

M: number of subjects with available data for the considered endpoint

Source: Adapted from Table 9.9 in the CSR of GRC88 (STN 103914/6208.5005)

Subgroup Analyses

Rates of fever between Group 1 and Group 2 were similar in demographic subgroup analyses: among subjects 6 to < 24 months of age, rates were 12.05% and 15.66%, respectively; among subjects 24 to < 36 months of age, rates were 10.38% and 7.52%, respectively. The younger age group did have higher rates of fever in general, and more grade 3 fevers; however these higher fever rates did not correlate with an increase in actions taken for the fever, such as medication use, contact with a health care provider, or hospitalization. A subanalysis by gender showed that the fever rates between Group 1 and Group 2 were similar within the female subgroup (Group 1, 13.04% of subjects; Group 2, 13.45% of subjects) and the male subgroup (Group 1, 9.65% of subjects; Group 2, 10.87% of subjects). A subanalysis by race showed that the fever rate differences between Group 1 and Group 2 were similar in the white subgroup (Group 1, 12.1% of subjects and Group 2, 11.9% of subjects) but differed between treatment groups for subjects in the non-white group, with fever rates trending higher in Group 2, (Group 1, 8.3% of subjects and Group 2 15.4% of subjects). Conclusions which can be drawn from these subgroup analyses are limited because they are post-hoc, and the study was not powered to demonstrate non-inferiority in these subgroups.

Table 6. Comparison of fever rates^a: 0.25-mL dose group vs. 0.5-mL dose group: Subgroup Analyses

Subgroup	Group 1 (0.25-mL dose) (N ^b =949)	Group 2 (0.5-mL dose) (N ^b =992)	Group 2 – Group 1
	Fever Rate (n ^c /M ^d)	Fever Rate (n ^c /M ^d)	Difference in Fever Rates (95% CI)
Total	11.3% (101/893)	12.2% (113/930)	0.8% (-2.1%, 3.8%)
After dose 1	8.1% (72/888)	8.0% (74/923)	Each subgroup is not powered to demonstrate non-inferiority
After dose 2	6.9% (33/475)	10.3% (49/478)	
6 to <24 months	12.0% (60/498)	15.7% (83/530)	
24 to <36 months	10.4% (41/395)	7.5% (30/400)	
Female	13.0% (57/437)	13.4% (62/461)	
Male	9.6% (44/456)	10.9% (51/469)	
White	12.1% (83/685)	12.0% (83/694)	
Non-White	8.3% (14/169)	15.4% (29/188)	

a: Rate of any fever (temperature ≥ 100.4 F [38.0 C]) during the 7 days after either vaccination (Dose 1 and Dose 2 combined)

b: Based on safety analysis set (subjects who received at least one dose of vaccines)

c: number of subjects experienced fever during 7 days after vaccination

d: number of subjects having valid temperature data during 7 days of vaccination

Source: Adapted from the Tables 5.1, 6.3, 29 (appendix 15), and 30 (appendix 15) in the CSR of GRC88, and Tables 9.12, 9.13, 9.14, and 9.15 in the addendum report of GRC88 (STN 103914/6208.0)

b) Pediatrics

Fluzone-QIV is currently approved for use in persons 6 months of age and older. The approved single dose volume of Fluzone-QIV in children 6 months to < 36 months of age is 0.25-mL, and in all persons 3 years of age and older, the approved single dose volume is 0.5-mL. The purpose of this supplement is to change the approved single dose volume to include use of the 0.5-mL dose in all persons 6 months of age and older. SP received a partial waiver for infants < 6 months of age based on the reasoning that Fluzone-QIV would provide no meaningful therapeutic benefit over vaccination at < 6 months of age, and these vaccines are unlikely to be used by a substantial number of infants < 6 months of age (Section 505B(a)(4)(A)iii of the Food Drug and Cosmetic Act). SP has previously fulfilled all pediatric study requirements for Fluzone-QIV product and submitted this supplement to establish a universal dose of 0.5-mL Fluzone-QIV for individuals 6 months and older. The study results were discussed during a November 14, 2018, meeting of the FDA Pediatric Review Committee. The committee agreed with SP's plan for a partial waiver for infants < 6 months of age because the product fails to represent a meaningful therapeutic benefit over existing therapies. The committee also concurred that the GRC88 clinical study met the non-inferiority criterion for occurrence of fever as an adverse reaction and showed comparable immune responses between 0.5-mL and 0.25-mL doses. The committee also agreed that the study supported inclusion of the 0.5-mL Fluzone-QIV dose for children 6 months to < 36 months in the product labeling.

c) Bioresearch Monitoring Review

Bioresearch Monitoring (BiMo) inspections were issued for four clinical study sites that participated in the conduct of the Study GRC88. The inspections did not reveal significant problems that would have impacted the outcomes submitted in this supplement.

d) Clinical Serology Assays

The HAI (hemagglutination inhibition) assay is an appropriate method to measure influenza virus vaccine responses in clinical trials, as these antibody titers are a marker of protection in vaccinated populations. The HAI assay was thus used in the GRC88 clinical trial to measure antibody titers against A/H1N1, A/H3N2 and B influenza viruses. The current HAI assay was validated at SP's Global Clinical Immunology (GCI) facility in Swiftwater, PA location in 2010, and the validation study for this facility was reviewed under STN 103914/5574. The HAI assay for this study was performed at (b) (4) after the assay was successfully transferred from the GCI facility to (b) (4). The HAI assay performed at (b) (4) and GCI yielded comparable results. Hence, (b) (4) was considered suitable to perform the influenza virus vaccine HAI assay as described in TSOP.119.011 for detection and quantitation of anti-influenza virus antibodies in clinical human serum samples for the GRC88 clinical study.

7. Safety

All safety analyses were conducted with the Safety Analysis Set, which included all subjects who received either study vaccine. A total of 1950 subjects were enrolled, of whom 1941 (99.5%) were vaccinated and included in the safety analysis. The collection of safety data included any immediate Adverse Events (AEs) within 20 minutes of vaccine administration, solicited local and systemic reactions from Day 0-7, and unsolicited AEs and SAEs from Visit 1-2 for subjects receiving one dose of vaccine and from Visit 1-3 for subjects receiving two doses of vaccine. Participants were monitored for unsolicited adverse events for 28 days after each dose and for serious adverse events (SAEs) during the 6 months following the last dose.

Because of concerns regarding the integrity of safety data collected at Site 009, an additional safety analysis was conducted which excluded data collected at this site, and results of that analysis were similar to those of the Safety Analysis Set.

Immediate unsolicited AEs (within 20 minutes of injection) were reported by 2 (0.2%) subjects in Group 1 and no subjects in Group 2. After any vaccination, similar percentages of subjects in Group 1 (645 [71%] subjects) and Group 2 (698 [74.2%] subjects) experienced a solicited reaction. Within the 28 day follow-up period following the final vaccination, AEs leading to discontinuation occurred in 3 subjects (0.3%) in Group 1 and no subjects in Group 2.

After any vaccination, 5 immediate AEs (within 20 minutes of vaccination) were experienced between a total of 2 (0.2%) subjects in Group 1 (diarrhea in one subject and venipuncture site bruising, erythema, pain and swelling in the other subject). No subjects in Group 2

experienced immediate AEs. None of these immediate unsolicited AEs led to study discontinuation.

Solicited injection site reactions were reported by 480 (52.8%) subjects in Group 1 and 533 (56.8%) subjects in Group 2. For both vaccine groups, tenderness was the most frequently reported solicited injection site reaction (Group 1, 430 [47.3%] subjects; Group 2, 473 [50.4%] subjects), followed by redness (Group 1, 210 [23.1%] subjects; Group 2, 228 [24.3%] subjects) and swelling (Group 1, 117 [12.9%] subjects; Group 2, 138 [14.7%] subjects). Results were similar for subjects who received 1 or 2 doses of vaccine. Most subjects had solicited injection site reactions with onsets between Day 0 and Day 3 and lasting 3 days or fewer.

Rates of solicited systemic reactions were similar in both groups (Group 1, 533 [58.6%] subjects; Group 2, 561 [59.6%] subjects). Solicited systemic reactions trended higher in subjects who received 2 doses of study vaccine (Group 1, 61.8%; Group 2, 62.6%) than subjects who received 1 dose of study vaccine (Group 1, 54.7%; Group 2, 56.0%). Irritability (Group 1, 430 [47.4%] subjects; Group 2, 457 [48.6%] subjects) was the most frequently reported solicited systemic reaction in both vaccine groups. Abnormal crying (Group 1, 302 [33.3%] subjects; Group 2, 321 [34.1%] subjects), drowsiness (Group 1, 290 [31.9%] subjects; Group 2, 294 [31.3%] subjects), and loss of appetite (Group 1, 248 [27.3%] subjects; Group 2, 266 [28.3%] subjects) were experienced by similar percentages of subjects in each vaccine group. Any fever was experienced by 101 (11.3%) subjects in Group 1 and 113 (12.2%) subjects in Group 2. The majority of solicited systemic reactions were Grade 1 or Grade 2 in intensity, with no imbalances between the vaccine groups in rates of Grade 3 reactions. Solicited systemic reactions occurred within 3 days of vaccination in most subjects and lasted for 3 days or fewer.

After any vaccine injection, rates of unsolicited AEs trended slightly higher in Group 1 subjects (43.9%) than in Group 2 subjects (39.7%). The most frequently reported unsolicited AEs after any vaccination were in the Infections and infestations SOC (Group 1, 193 [20.3%] subjects; Group 2, 201 [20.3%] subjects), followed by respiratory, thoracic and mediastinal disorders (Group 1, 150 [15.8%] subjects; Group 2, 154 [15.5%] subjects). The most commonly reported unsolicited AEs were cough (Group 1, 104 [11.0%] subjects; Group 2, 103 [10.4%] subjects) and rhinorrhea (Group 1, 72 [7.6%] subjects; Group 2, 71 [7.2%] subjects). The majority of unsolicited AEs were Grade 1 or 2 in intensity. Grade 3 unsolicited non-serious AEs were experienced by 62 (6.5%) subjects in Group 1 and 65 (6.6%) subjects in Group 2. There were no febrile seizures reported in this study.

Serious adverse events were collected between Visit 1 and Visit 2 for subjects receiving 1 dose, and between Visit 1 and Visit 3 for subjects receiving 2 doses of the vaccine. No deaths were reported during the study. A total of 5 (0.5%) subjects in Group 1 and 5 (0.5%) subjects in Group 2 experienced a total of 10 SAEs, none of which were considered related to vaccination by the clinical reviewer.

In Group 1, one subject discontinued from the study due to an SAE of pneumonia that was diagnosed 21 days after 1 dose of the study vaccine; the pneumonia was considered unrelated

to the study vaccine. The other SAEs in Group 1 included: a hospitalization for a known diagnosis of tracheomalacia, a hospitalization for tonsillitis 27 days after the study vaccine, a hospitalization for acute viral upper respiratory infection 9 days following study vaccine, and a diagnosis of chronic urticaria (defined as a SAE per protocol) with ongoing symptoms for more than 6 weeks prior to study vaccination and a rash and wheals 3 days after 1 dose of study vaccine. These four subjects with SAEs continued in the study, and the event of chronic urticaria was considered related to the study vaccine by the sponsor but not by the clinical reviewer because its onset preceded study vaccination.

In Group 2, all five of the subjects who experienced an SAE continued in the study, and none of the events were considered related to the study vaccine. The SAEs in Group 2 included: an abscess of the right medial thigh 13 days following study vaccine that resolved followed by a cellulitis on the right buttocks requiring hospitalization, a hospitalization for dehydration due to herpangina that started 6 days following study vaccine, a hospitalization for RSV bronchiolitis 19 days following study vaccine, a hospitalization for management of an accidental clonidine ingestion 27 days following study vaccine, and a hospitalization for pneumonia 28 days following study vaccine.

Adverse events of special interest (AESI) were captured as SAEs. There was 1 (0.1%) AESI (chronic urticaria [considered related to vaccination by the Investigator]) reported during the study in a subject who received 1 dose of study vaccine.

Overall 0.5-mL dose of Fluzone-QIV was well tolerated in children 6 to 35 months of age, and no safety signals were observed in the clinical study. Furthermore, analysis of safety data does not raise any safety concerns for use of this dose of the vaccine in individuals 6-35 months of age.

8. Advisory Committee Meeting

This sBLA was not discussed at a VRBPAC meeting because review of this submission did not identify concerns or issues for which the Agency would have benefited from an advisory committee discussion.

9. Other Relevant Regulatory Issues

None

10. Labeling

Section 8 of the PI “Use In Specific Populations” was revised to comply with the Requirements for Pregnancy and Lactation Labeling, referred to as the “Pregnancy and Lactation Labeling Rule” (PLLR), published by FDA in December 2014. There were several inconsistencies and typographical errors noted in Section 6.2 (Post marketing Experience) of

the draft Fluzone-QIV PI, which were addressed appropriately by SP. Section 6.2 of the PI was also updated by adding postmarketing data for Fluzone-QIV. SP submitted a revised Fluzone-QIV PI addressing CBER's comments which was found to be acceptable.

Four study sites of the GRC88 clinical study were found to have issues either with safety data integrity [site 009 (n=31)] or with vaccine storage equipment temperature excursion [sites 016 (n=59), 019 (n=26), and 021 (n=7)]. The immunogenicity analysis were conducted excluding subjects from three sites with "temperature excursion," and revised data were included in Section 14.4 of the PI. Tables in the PI containing data were updated to include 0.25-mL or 0.5-mL dose used for the studies.

The revised Fluzone-QIV PI with data from this supplement in support of the inclusion of 0.5-mL dose of the vaccine in children 6 to < 36 months of age was reviewed by relevant members of the review committee, including clinical, statistical, epidemiology and APLB reviewers. The revised Fluzone-QIV PI incorporates information from the GRC88 clinical study into the "Clinical Studies" as well as "Adverse Reactions" sections.

Minor changes were made throughout the PI to improve clarity and consistency. The review committee concurs that the PI submitted on January 11, 2019, is acceptable. The revised carton labels, submitted on January 11, 2019, were reviewed and found to be acceptable. APLB found the prescribing information and carton labels to be acceptable from a promotional and comprehension perspective. The container labels were not submitted in this supplement, as no changes were made to the container labels that was previously approved under STN 103914/6200 (2018-2019 annual strain change supplement).

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

It is the consensus of the review committee to recommend approval of this application for the use of a 0.5-mL dose of Fluzone-QIV in children 6 to < 36 months of age for active immunization for the prevention of disease caused by the influenza A subtype viruses and type B viruses contained in the vaccine.

b) Risk/ Benefit Assessment

Data submitted in this supplement establish the safety and effectiveness of the 0.5-mL dose of Fluzone-QIV for children ages 6 to < 36 months for prevention of influenza caused by influenza viral types/subtypes included in the vaccine. The risks of vaccination with the 0.5-mL dose of Fluzone-QIV in children 6 to < 36 months of age have been found to be minimal and justified by substantial clinical benefit in terms of prevention of influenza disease. Thus, the overall risk/benefit profile of this product is favorable in this age group.

c) Recommendation for Postmarketing Risk Management Activities

No safety issues were identified to warrant a Risk Evaluation and Mitigation Strategy (REMS) or a new Postmarketing Requirement (PMR).

d) Recommendation for Postmarketing Activities

No changes to the submitted pharmacovigilance plan for Fluzone-QIV are recommended based on the information contained in this application.

e) Pharmacovigilance plan

The review committee concurs with SP's proposed changes to Section 6.2, Postmarketing Experience, of the PI. Routine surveillance, including review of the Vaccine Adverse Event Reporting System (VAERS), the manufacturer's periodic submissions, data mining, literature searches, and review of postmarketing studies, has not identified any new safety concerns.

References:

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2. Schanzer D, Langley J, Tam T. Hospitalization Attributable to Influenza and Other Viral Respiratory Illnesses in Canadian Children. *Pediatr Infect Dis J* 25:795-800, 2006.
3. CDC (Centers for Disease Control and Prevention). Influenza vaccination coverage among children aged 6-23 months--United States, 2005-06 influenza season. *MMWR* 56(37):959-63, 2007.
4. Poehling KA, Edwards KM, Weinberg GA, Szilagyi P et al, for the New Vaccine Surveillance Network. The under-recognized burden of influenza in young children. *NEJM* 355:31-40, 2006.