Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Statistical Review and Evaluation	
Application Type	Efficacy Supplement
STN	103914/6208
CBER Received Date	March 30, 2018
PDUFA Goal Date	January 28, 2019
Division / Office	Division of Vaccines and Related Product Applications Office of Vaccines Research and Review (OVRR)
Committee Chair	Goutam Sen
Clinical Reviewer(s)	Susan Wollersheim
Project Manager(s)	Richard Daemer & Rebekah Wiesmann
Priority Review	No
Reviewer Name(s)	Sang Ahnn, VEB/DB/OBE
Supervisory Concurrence	Tsai-Lien Lin, Branch Chief, VEB/DB/OBE
Applicant	Sanofi Pasteur Inc.
Established Name	Influenza Virus vaccine (4-valent)
Trade Name	Fluzone Quadrivalent
Pharmacologic Class	Vaccine
Formulation	0.5-mL suspension
Dosage Form(s) and Route(s) of Administration	Intramuscular injection of 0.5-mL/dose
Dosing Regimen	1 or 2-dose (0, 28 days)
Indication(s) and Intended Population(s)	Prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine for children 6 to 36 months of age

Table of Contents

List of Tables

1. Executive Summary

This submission includes the applicant's clinical study report (CSR) of a randomized Phase IV study (GRC88) comparing the safety and immunogenicity profiles of a 0.5-mL dose of Fluzone Quadrivalent vaccine (15 µg hemagglutinin [HA] per strain) to those of a 0.25-mL dose (7.5 µg HA per strain). The purpose of this submission is to offer both the 0.25-mL and 0.5-mL dose options for use in children 6 months to < 36 months of age.

GRC88 was a Phase IV, randomized, observer-blinded, 2-arm, multi-center (38 U.S. centers) study to evaluate the safety and immunogenicity of 2 different dose levels of Fluzone Quadrivalent vaccine in healthy children 6 to < 36 months of age. A total of 1950 subjects were randomly assigned at a 1:1 ratio to one of the two groups: Group 1 [0.25 mL of Fluzone Quadrivalent vaccine (n=955)] or Group 2 [0.5 mL of Fluzone Quadrivalent vaccine (n=995)]. Randomization was stratified by center and age (6 to <24 months and 24 to <36 month). Among the 1950 randomized subjects, 1460 (74.9%) were randomly assigned to the immunogenicity subset: 715 subjects in Group 1 and 745 subjects in Group 2. Subjects received either 1 or 2 dose(s) of Fluzone Quadrivalent vaccine(s) based on the recommendation of the Advisory Committee on Immunization Practices (ACIP) guidance (a second dose of vaccine was administered during Visit 2 (28 [window, 28–35] days after Visit 1).

The primary objective of this study was to compare the rate of any fever (temperature ≥ 100.4 F [38.0 C]) during the 7 days following either the 0.5-mL or the 0.25-mL dose vaccination (Dose 1 and Dose 2 combined) in subjects 6 to < 36 months of age. Non-inferiority [non-inferior safety of 0.5-mL dose (Group 2) to 0.25-mL dose (Group 1)] criterion was defined as the upper bound of the 2-sided 95% CI of the fever rate difference (Group 2 - Group 1) being < 5%.

The fever rate of 0.5-mL dose group (12.2%) was non-inferior to the fever rate of 0.25-mL dose group (11.3%) according to the pre-specified non-inferiority safety criterion; difference in fever rates = 0.8% (95% CI: -2.1%; **3.8%**).

A total of 10 SAEs were reported (5 in each group), and 1 SAE (chronic urticaria) in the 0.25-mL dose group was declared as vaccine-related by the applicant. No death was reported.

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 Seroconversion (SC) rate differences after the final vaccination in subjects 6 to < 36 months of age. Non-inferiority criteria were (a) the lower bound of the 2-sided 95% CI of the GMT ratio ($GMT_{0.5mL}$ / $GMT_{0.25mL}$) being > 0.67 for each of the 4 virus strains, *and* (b) the lower bound of the 2-sided 95% CI of the difference in SC rates ($SC\ rate_{0.5mL}$ - $SC\ rate_{0.25mL}$) being > -10% for each of the 4 virus strains.

As expected, the 0.5-mL dose vaccine induced antibody responses that were non-inferior to those of the 0.25-mL dose vaccine according to the pre-specified non-inferiority immunogenicity criteria, with respect to all 4 strains contained in the vaccine.

2. Clinical and Regulatory Background

Please refer to this section in the clinical reviewer's review.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Data Integrity

In this study there were four centers found to have problems either in 'integrity of safety data' [site 009 (n=31)] or in 'temperature excursion of the vaccine storage equipment' [sites 016 (n=59), 019 (n=26), and 021 (n=7)].

5. Sources of Clinical data and Other Information Considered in the Review

5.1 Review Strategy

This submission includes the clinical study report of GRC88. Statistical aspects of the safety and immunogenicity analyses were reviewed.

5.2 BLA Documents that Serve as the Basis for the Statistical Review

This submission (STN 103914/6208) was received on 3/30/2018 and is located in the EDR. The Clinical Study Reports (CSR), electronic datasets, and Case Report Forms (CRF) for GRC88 are located in section 5.3.5.1 of this submission. STN 103914/6208.0 and STN 103914/6208.5005 were reviewed.

6. Discussion of Individual Studies/Clinical Trials

6.1 GRC88

Title of the study: "Safety and Immunogenicity of Fluzone® Quadrivalent Vaccine Administered to Healthy Children 6 to < 36 Months of Age"

Date of study initiation: 9/23/2016
Date of study completion: 3/6/2017

6.1.1 Objectives

The primary objective of this study was to compare the rate of any fever (temperature ≥ 100.4 F [38.0 C]) following the 0.5-mL dose to that following the 0.25-mL dose during the 7 days after either vaccination (Dose 1 and Dose 2 combined) in subjects 6 to < 36 months of age.

The secondary objective was to compare antibody responses induced by the 0.5-mL dose to those induced by the 0.25-mL dose as assessed by geometric mean titer (GMT) ratios and seroconversion (SC) rate differences after the final vaccination in subjects 6 to < 36 months of age. [Geometric mean titers: The HAI GMTs (for each of the 4 strains) at 28 (window, 28–35) days after the final vaccination; Seroconversion rates: The percentages of subjects with either a pre-vaccination titer < 10 (1/dil) and a post-vaccination titer ≥ 40 (1/dil), or a pre-vaccination titer ≥ 10 (1/dil) and a ≥ 4 fold increase in post-vaccination titer at 28 (window, 28‑35) days after the final vaccination.]

6.1.2 Design Overview

This study (GRC88) was a Phase IV, randomized, observer-blinded, 2-arm, multi-center (38 centers in the U.S.) study of a planned 2190 subjects to evaluate the safety and immunogenicity of 2 different dose levels [0.5-mL dose (15 µg hemagglutinin per strain) vs. 0.25-mL dose (7.5 µg HA per strain)] of Fluzone Quadrivalent vaccine in healthy children 6 to < 36 months of age.

A total of 1950 subjects were randomly assigned in a 1:1 ratio to either 1 of the 2 groups: Group 1 [0.25 mL of Fluzone Quadrivalent vaccine (n=955)] or Group 2 [0.5 mL of Fluzone Quadrivalent vaccine (n=995)]. Randomization was stratified by center and age (6 to <24 months and 24 to <36 month). Among the 1950 randomized subjects, 1460 (74.9%) were randomly assigned to the immunogenicity subset: 715 subjects in Group 1 and 745 subjects in Group 2. Subjects received either 1 or 2 dose(s) of Fluzone Quadrivalent vaccine(s) based on the recommendation of the Advisory Committee on Immunization Practices (ACIP) guidance (a second dose of vaccine was administered during Visit 2 (28 [window, 28–35] days after Visit 1).

6.1.3 Population

Among a total of 1950 randomized subjects, 1941 subjects (949 in Group 1 and 992 in Group 2) received at least one dose of vaccine and were included in the Safety Analysis Set.

Among 1460 subjects randomly assigned to the immunogenicity subset, 1068 subjects (502 in Group 1 and 525 in Group 2) were included in the Per-Protocol Analysis Set for immunogenicity

.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Group 1: Fluzone Quadrivalent vaccine, No Preservative, Pediatric Dose (0.25-mL dose), 2016–2017 formulation, Containing 7.5 µg hemagglutinin (HA) of each antigen, Intramuscular injection.

Group 2: Fluzone Quadrivalent vaccine, No Preservative (0.5-mL dose), 2016–2017 formulation Liquid – pre-filled syringes, Containing 15 µg hemagglutinin (HA) of each antigen, Intramuscular injection.

6.1.6 Sites and centers

This study was conducted at 38 study centers in the U.S.

6.1.7 Surveillance/Monitoring

Please refer to this section in the clinical reviewer's review.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint: Rate of any fever (temperature ≥ 100.4 F [38.0 C]) during the 7 days after either vaccination (Dose 1 and Dose 2 combined). Non-inferiority [non-inferior safety of 0.5-mL dose (Group 2) to 0.25-mL dose (Group 1)] criterion was the upper bound of the 2-sided 95% CI of the fever rate difference (Group 2 - Group 1) being < 5%.

Secondary endpoints: (a) Geometric mean titers: The HAI GMTs (for each of the 4 strains) at 28 (window, 28–35) days after the final vaccination; *and* (b) Seroconversion rates: The percentages of subjects with either a pre-vaccination titer < 10 (1/dil) and a post-vaccination titer ≥ 40 (1/dil), or a pre-vaccination titer ≥ 10 (1/dil) and a ≥ 4 fold increase in post-vaccination titer at 28 (window, 28‑35) days after the final vaccination. Non-inferiority criteria were (a) the lower bound of the 2-sided 95% CI of the GMT ratio ($GMT_{0.5mL}$ / $GMT_{0.25mL}$) being > 0.67 for each of the 4 virus strains, *and* (b) the lower bound of the 2-sided 95% CI of the difference in SC rates ($SC\ rate_{0.5mL}$ - $SC\ rate_{0.25mL}$) being > -10% for each of the 4 virus strains.

6.1.9 Statistical Considerations and Statistical Analysis Plan

The primary hypothesis tested was

H_0: $FR_{0.5mL} - FR_{0.25mL} \geq 5\%$

where FR = Rate of any fever (temperature ≥ 100.4 F [38.0 C]) during the 7 days after either vaccination (Dose 1 and Dose 2 combined). Equivalently, non-inferiority [non-inferior safety of 0.5-mL dose (Group 2) to 0.25-mL dose (Group 1)] criterion was the upper bound of the 2-sided 95% CI of the fever rate difference (Group 2 - Group 1) being < 5%.

The secondary hypotheses tested were (for each strain)

H_0: $GMT_{0.5mL} / GMT_{0.25mL} \leq 0.67$, *and*

H_0: SC $rate_{0.5mL}$ - SC $rate_{0\ 25mL} \leq -10\%$

where GMT = HAI GMT (for each of the 4 strains) at 28 (window, 28–35) days after the final vaccination, and SC = Seroconversion rates [The percentages of subjects with either a pre-vaccination titer < 10 (1/dil) and a post-vaccination titer ≥ 40 (1/dil), or a pre-vaccination titer ≥ 10 (1/dil) and a ≥ 4 fold increase in post-vaccination titer at 28 (window, 28‑35) days after the final vaccination]. Equivalently, non-inferiority criteria were (a) the lower bound of the 2-sided 95% CI of the GMT ratio ($GMT_{0.5mL}$ / $GMT_{0.25mL}$) being > 0.67 for each of the 4 virus strains, *and* (b) the lower bound of the 2-sided 95% CI of the difference in SC rates (SC $rate_{0.5mL}$ - SC $rate_{0.25mL}$) being > -10% for each of the 4 virus strains.

6.1.10 Primary Analyses (Safety Analyses based on Fever Rates)

Table 1 presents the comparison of the fever rates between Group 1 (0.25-mL dose) and Group 2 (0.5-mL dose) for subjects in the Safety Analysis Set. Non-inferior safety of 0.5-mL dose compared to 0.25-mL dose was demonstrated according to the pre-specified non-inferiority criterion of the upper bound of the 2-sided 95% CI of the fever rate difference (Group 2 - Group 1) being < 5%.

Table 1. Comparison of fever rates[$]: 0.25-mL dose group vs. 0.5-mL dose group

Group 1 (0.25-mL dose) ($N^{@}$=949)	**Group 2 (0.5-mL dose)** ($N^{@}$=992)	Group 2 – Group 1
Fever Rate ($n^{\wedge}/M^{\&}$)	Fever Rate ($n^{\wedge}/M^{\&}$)	Difference in Fever Rates (95% CI)
11.3% (101/893)	12.2% (113/930)	0.8% (-2.1%, 3.8%)

$ Rate of any fever (temperature ≥ 100.4 F [38.0 C]) during the 7 days after either vaccination (Dose 1 and Dose 2 combined)
@ Based on safety analysis set (subjects who received at least one dose of vaccines)
^ number of subjects experienced fever during 7 days after vaccination
& number of subjects having valid temperature data during 7 days of vaccination
Source: Extracted from the applicant's Table 5.1 in the CSR of GRC88 (STN 103914/6208.0)

In this study there were four centers found to have problems either in 'integrity of safety data' [site 009 (n=31)] or in 'temperature excursion of the vaccine storage equipment' [sites 016 (n=59), 019 (n=26), and 021 (n=7)]. Comparison of fever rates excluding those four sites also demonstrated the non-inferior safety of 0.5-mL dose compared to 0.25-mL dose as is shown in Table 2.

Table 2. Comparison of fever rates[$]: 0.25-mL dose group vs. 0.5-mL dose group (Sites 009, 016, 019, and 021 excluded)

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)
11.8% (99/837)	12.6% (110/874)	0.8% (-2.4%, 3.9%)

$ Rate of any fever (temperature ≥ 100.4 F [38.0 C]) during the 7 days after either vaccination (Dose 1 and Dose 2 combined)
@ Based on safety analysis set (subjects who received at least one dose of vaccines)
^ number of subjects experienced fever during 7 days after vaccination
& number of subjects having valid temperature data during 7 days of vaccination
Source: Reviewer-generated.

6.1.11 Secondary Analyses (Immunogenicity Analyses based on GMTs and SCs)

Table 3 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 ($GMT_{0.5mL}$ / $GMT_{0.25mL}$) being > 0.67 for each of the 4 virus strains.

Table 3. Comparison of GMTs[$]: 0.25-mL dose group vs. 0.5-mL dose group

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)

$ Post-final vaccination GMTs (28-35 days after the final vaccination)
@ Based on Per-protocol Analysis set
& number of subjects with available data for the considered endpoint
Source: Extracted from the applicant's Table 9.5 in the CSR of GRC88 (STN 103914/6208.5005)

Table 4 presents the comparison of seroconversion 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 ($SC\ rate_{0.5mL}$ - $SC\ rate_{0.25mL}$) being > -10% for each of the 4 virus strains.

Table 4. Comparison of seroconversion (SC) rates[$]: 0.25-mL dose group vs. 0.5-mL dose group

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)

$ Please see Section 6.1.8 for the definition of seroconversion rate
@ Based on Per-protocol Analysis set
& number of subjects with available data both at baseline and post-final vaccination for the considered endpoint
Source: Extracted from the applicant's Table 9.9 in the CSR of GRC88 (STN 103914/6208.5005)

6.1.12 Other Safety Analyses

A total of 10 SAEs were reported (5 in each group), and 1 SAE (chronic urticaria) in the 0.25-mL dose group was declared as vaccine-related by the applicant. No death was reported. Please see the clinical review for further discussion on safety.

6.1.13 Subgroup Analyses of the Primary Endpoint

Subgroup analyses of the primary endpoint [rate of any fever (temperature ⩾ 100.4 F [38.0 C]) during the 7 days after either vaccination (Dose 1 and Dose 2 combined)] were performed by dose (after dose 1 and after dose 2), age (6 to <24 months and 24 to <36 months), gender (female and male), and race (white and non-white).

Table 5. Comparison of fever rates[$]: 0.25-mL dose group vs. 0.5-mL dose group (Subgroup Analyses)

Subgroup	**Group 1 (0.25-mL dose)** (N[@]=949) Fever Rate (n[^]/M[&])	**Group 2 (0.5-mL dose)** (N[@]=992) Fever Rate (n[^]/M[&])	Group 2 – Group 1 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)	

$ Rate of any fever (temperature ≥ 100.4 F [38.0 C]) during the 7 days after either vaccination (Dose 1 and Dose 2 combined)
@ Based on safety analysis set (subjects who received at least one dose of vaccines)
^ number of subjects experienced fever during 7 days after vaccination
& number of subjects having valid temperature data during 7 days of vaccination

Source: Extracted from the applicant's Tables 5.1, 6.3, 29 (appendix 15), and 30 (appendix15) 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)

Higher fever rate observed in Group 2 among 6 to <24 months and among Non-whites may need further investigation [among non-whites, majority were black].

7. Integrated Overview of Efficacy

N/A

8. Integrated Overview of Safety

N/A

10. Conclusions

1. Non-inferior safety of 0.5-mL dose compared to 0.25-mL dose was demonstrated according to the pre-specified non-inferiority criterion of the upper bound of the 2-sided 95% CI of the fever rate difference (Group 2 - Group 1) being < 5%.
2. 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 ($GMT_{0.5mL}$ / $GMT_{0.25mL}$) being > 0.67 for each of the 4 virus strains.
3. 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 (SC $rate_{0.5mL}$ - SC $rate_{0.25mL}$) being > -10% for each of the 4 virus strains.
4. In this study there were four centers found to have problems either in 'integrity of safety data' [site 009 (n=31)] or in 'temperature excursion of the vaccine storage equipment' [sites 016 (n=59), 019 (n=26), and 021 (n=7)]. Comparison of fever rates excluding those four sites also demonstrated the non-inferior safety of 0.5-mL dose compared to 0.25-mL dose.
5. Higher fever rate observed in Group 2 among 6 to <24 months and among Non-whites may need further investigation.