DEPARTMENT OF HEALTH AND HUMAN SERVICES

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:	STN 103914/5574.0
Product Name:	Fluzone® Quadrivalent Influenza Vaccine
Indication(s):	Active immunization of persons 6 months of age and older against influenza disease caused by influenza virus subtypes A and both influenza B lineages contained in the vaccine
Applicant:	Sanofi Pasteur Inc.
Date(s):	Date submitted: August 10, 2012 Action due date: June 10, 2013
Review Priority:	Standard
Statistical Branch:	Vaccine Evaluation Branch
Primary Statistical Reviewer:	Sang Ahnn
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EXECUTIVE SUMMARY

This supplemental BLA presents data to support licensure of a 4-strain formulation of Fluzone, Fluzone Quadrivalent, inactivated influenza vaccine, for active immunization of persons 6 months of age and older against influenza disease caused by influenza virus subtypes A and both influenza B lineages contained in the vaccine.

Clinical data presented in this supplement include two Phase III clinical trials, QIV-04 (immunogenicity study in subjects 6 months to <9 years of age) and QIV-03 (immunogenicity study in subjects 65 years of age and older) along with supportive data from a Phase II study, GRC43 (immunogenicity study in subjects 18 years of age and older). The focus of this review is on the two Phase III studies, QIV-04 and QIV-03.

RECOMMENDATION: For subjects 6 months to <9 years of age, noninferior immunogenicity of Fluzone Quadrivalent compared to Fluzone was shown for each of A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, based on the pre-specified noninferiority criteria [the lower bound for each of the four 95% CIs for the GMT ratios (Fluzone Quadrivalent/Fluzone) be > 0.67, and the lower bound for each of the four 95% CIs for the seroconversion rate differences (Fluzone Quadrivalent - Fluzone) be > -10.0%]. For subjects 65 years of age and older, noninferior immunogenicity of Fluzone Quadrivalent compared to Fluzone was shown for each of A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, based on the pre-specified noninferiority criterion [the lower bound for each of the four 95% CIs for the GMT ratios (Fluzone Quadrivalent/Fluzone) be > 0.67]. Therefore, study objectives appear to be met regarding immunogenic noninferiority of Fluzone Quadrivalent compared to Fluzone. There are no safety concerns based on the data submitted and reviewed.

QIV04

This was a Phase III, randomized, observer-blind, active-controlled, 3-arm, multi-center study with planned enrollment of 4,940 subjects in 2 age strata (6 months - <36 months and 3 years - <9 years of age). The primary objective of this study was to demonstrate non-inferior immune responses of Fluzone Quadrivalent [QIV] to licensed 2010-2011 Fluzone (containing the primary B strain) [TIV1] and investigational Fluzone (containing the alternate B strain) [TIV2] as assessed by geometric mean titer (GMT) ratios and seroconversion rate (SCR) differences after the final vaccination, separately within each age group (6 to < 36 months and 3 to < 9 years of age) and overall.

Three treatment groups were as follows:
[TIV1] Licensed 2010-2011 TIV containing the primary B strain (n=800 planned)
[TIV2] Investigational TIV containing the alternate B strain (n=800 planned)
[QIV] Investigational Quadrivalent Influenza Vaccine (QIV) (n=3,340 planned)

Blood samples were to be collected from all subjects prior to the first vaccination and 28 days following the final vaccination and assayed for immune response.

A total of 4,363 subjects 6 months - <9 years of age were randomized, and 4,013 subjects completed the study. Fifteen subjects were randomized but did not receive vaccine. A total of 4,348 randomized subjects were included in the Safety Analysis Set. The Per-Protocol (PP) Analysis Set included 2,339 subjects in the QIV group, 582 subjects in the 2010-2011 TIV group, and 599 subjects in the investigational TIV group.

Primary analysis of immunogenicity

The statistical criteria to show noninferior immune response to QIV compared to TIV were that the lower bound for each of the four 95% CIs for the GMT ratios (Fluzone Quadrivalent/Fluzone) be > 0.67, and the lower bound for each of the four 95% CIs for the seroconversion rate differences (Fluzone Quadrivalent - Fluzone) be > -10.0%. The comparators were subjects in the two Fluzone groups [TIV1 and TIV2] combined for A/H1N1 and A/H3N2 strains and subjects who received Fluzone with a matching B strain for the B/Brisbane and B/Florida strains.

The primary immunogenicity analyses were performed on the Per-Protocol population. The applicant performed the primary immunogenicity analyses as pre-specified, and the applicant's results (Tables 1 – 6) were verified by the reviewer. [Confidence intervals for the GMT ratios were calculated based on the normality assumption of log titers, and confidence intervals for the seroconversion rate differences were calculated based on the normal approximation to the binomial distribution.]

Table 1. Primary immunogenicity results for all age groups (6 months - <9 years of age): GMT ratio

Antigen strain	GMT ratio[QIV/TIV] (95% CI)	Non-inferiority of QIV to TIV (LB of CI of GMT ratio > 0.67)
H1N1	1.03 (0.93; 1.14)	Yes
H3N2	0.99 (0.91; 1.08)	Yes
B/Brisbane	1.34 (1.20; 1.50)	Yes
B/Florida	1.06 (0.94; 1.18)	Yes

* For B/Brisbane, GMT ratio of QIV/TIV1. For B/Florida, GMT ratio of QIV/TIV2

Table 2. Primary immunogenicity results for subjects 6 months - <36 months of age: GMT ratio

Antigen strain	GMT ratio[QIV/TIV] (95% CI)	Non-inferiority of QIV to TIV (LB of CI of GMT ratio > 0.67)
H1N1	1.05 (0.89; 1.23)	Yes
H3N2	0.92 (0.82; 1.04)	Yes
B/Brisbane	1.33 (1.12; 1.59)	Yes
B/Florida	1.10 (0.94; 1.28)	Yes

* For B/Brisbane, GMT ratio of QIV/TIV1. For B/Florida, GMT ratio of QIV/TIV2

Table 3. Primary immunogenicity results for subjects 3 years - <9 years of age: GMT ratio

Antigen strain	GMT ratio[QIV/TIV] (95% CI)	Non-inferiority of QIV to TIV (LB of CI of GMT ratio > 0.67)
H1N1	1.02 (0.90; 1.16)	Yes
H3N2	1.05 (0.95; 1.17)	Yes
B/Brisbane	1.36 (1.17; 1.57)	Yes
B/Florida	1.02 (0.89; 1.17)	Yes

* For B/Brisbane, GMT ratio of QIV/TIV1. For B/Florida, GMT ratio of QIV/TIV2

Table 4. Primary immunogenicity results for all age groups (6 months - <9 years of age): Seroconversion Rate (SCR) difference

Antigen strain	SCR(%) difference[QIV-TIV] (95% CI)	Non-inferiority of QIV to TIV (LB of CI of SCR difference > -10%)
H1N1	0.9 (-0.9;3.0)	Yes
H3N2	3.8 (1.4;6.3)	Yes
B/Brisbane	10.7 (6.4;15.1)	Yes
B/Florida	2.0 (-2.2;6.4)	Yes

* For B/Brisbane, SCR difference of QIV-TIV1. For B/Florida, SCR difference of QIV-TIV2

Table 5. Primary immunogenicity results for all age groups (6 months – <36 months of age): Seroconversion Rate (SCR) difference

Antigen strain	SCR(%) difference[QIV-TIV] (95% CI)	Non-inferiority of QIV to TIV (LB of CI of SCR difference > -10%)
H1N1	1.6 (-1.6;5.1)	Yes
H3N2	2.9 (0.4;5.9)	Yes
B/Brisbane	7.1 (0.5;14.1)	Yes
B/Florida	4.0 (-2.9;11.0)	Yes

* For B/Brisbane, SCR difference of QIV-TIV1. For B/Florida, SCR difference of QIV-TIV2

Table 6. Primary immunogenicity results for all age groups (3 years - <9 years of age): Seroconversion Rate (SCR) difference

Antigen strain	SCR(%) difference[QIV-TIV] (95% CI)	Non-inferiority of QIV to TIV (LB of CI of SCR difference > -10%)
H1N1	0.6 (-1.6;3.0)	Yes
H3N2	4.2 (0.7;7.9)	Yes
B/Brisbane	12.9 (7.4;18.6)	Yes
B/Florida	0.6 (-4.5;6.0)	Yes

* For B/Brisbane, SCR difference of QIV-TIV1. For B/Florida, SCR difference of QIV-TIV2

Secondary analysis of immunogenicity

For B/Brisbane and B/Florida strains, the statistical criteria to show higher immune response to QIV compared to TIV were that the lower bound for each of the two 95% CIs for the GMT ratios (Fluzone Quadrivalent/Fluzone) be > 1.5, and the lower bound for each of the two 95% CIs for the seroconversion rate differences (Fluzone Quadrivalent - Fluzone) be > 10.0%. The comparators were subjects who did not receive Fluzone with a matching B strain.

The secondary immunogenicity analyses were performed on the Per-Protocol population. The applicant performed the secondary immunogenicity analyses as pre-specified, and the applicant's results (Tables 7 – 12) were verified by the reviewer:

Table 7. Secondary immunogenicity results for all age groups (6 months - <9 years of age): GMT ratio

Antigen strain	GMT ratio[QIV/TIV*] (95% CI)	Superiority of QIV to TIV (LB of CI of GMT ratio > 1.5)
B/Brisbane	4.42 (3.94; 4.97)	Yes
B/Florida	3.79 (3.39; 4.23)	Yes

* For B/Florida, GMT ratio of QIV/TIV1. For B/Brisbane, GMT ratio of QIV/TIV2

Table 8. Secondary immunogenicity results for subjects 6 months - <36 months of age: GMT ratio

Antigen strain	GMT ratio[QIV/TIV*] (95% CI)	Superiority of QIV to TIV (LB of CI of GMT ratio > 1.5)
B/Brisbane	6.09 (5.13; 7.23)	Yes
B/Florida	4.22 (3.62; 4.93)	Yes

* For B/Florida, GMT ratio of QIV/TIV1. For B/Brisbane, GMT ratio of QIV/TIV2

Table 9. Secondary immunogenicity results for subjects 3 years - <9 years of age: GMT ratio

Antigen strain	GMT ratio[QIV/TIV*] (95% CI)	Superiority of QIV to TIV (LB of CI of GMT ratio > 1.5)
B/Brisbane	3.54 (3.04; 4.13)	Yes
B/Florida	3.63 (3.16; 4.16)	Yes

* For B/Florida, GMT ratio of QIV/TIV1. For B/Brisbane, GMT ratio of QIV/TIV2

Table 10. Secondary immunogenicity results for all age groups (6 months - <9 years of age): Seroconversion Rate (SCR) difference

Antigen strain	SCR(%) difference[QIV-TIV*] (95% CI)	Superiority of QIV to TIV (LB of CI of SCR difference > 10%)
B/Brisbane	51.8 (47.9; 55.3)	Yes
B/Florida	48.2 (44.3; 51.6)	Yes

* For B/Florida, SCR difference of QIV-TIV1. For B/Brisbane, SCR difference of QIV-TIV2

Table 11. Secondary immunogenicity results for all age groups (6 months – <36 months of age): Seroconversion Rate (SCR) difference

Antigen strain	SCR(%) difference[QIV-TIV*] (95% CI)	Superiority of QIV to TIV (LB of CI of SCR difference > 10%)
B/Brisbane	57.3 (51.5; 62.1)	Yes
B/Florida	50.8 (45.7; 54.8)	Yes

* For B/Florida, SCR difference of QIV-TIV1. For B/Brisbane, SCR difference of QIV-TIV2

Table 12. Secondary immunogenicity results for all age groups (3 years - <9 years of age): Seroconversion Rate (SCR) difference

Antigen strain	SCR(%) difference[QIV-TIV*] (95% CI)	Superiority of QIV to TIV (LB of CI of SCR difference > 10%)
B/Brisbane	47.9 (42.6; 52.7)	Yes
B/Florida	46.9 (41.6; 51.7)	Yes

* For B/Florida, SCR difference of QIV-TIV1. For B/Brisbane, SCR difference of QIV-TIV2

Safety

In subjects 6 months to < 36 months of age, SAEs occurred in 2.5% (30/1223) of the subjects in the QIV group, 1.3% (4/310) of the subjects in the 2010-2011 TIV group, and 3.2% (10/308) of the subjects in the investigational TIV group. Among the SAEs, 2 were considered (by the applicant) to be related to study vaccine: 1 in the QIV group (croup 3 days post-vaccination) and 1 in the investigational TIV group (febrile seizure 8 hours post-vaccination). One death (Subject 052-00197) occurred in the 2010-2011 TIV group (drowning 43 days post-vaccination), and was not considered related to study vaccine.

In subjects 3 years to < 9 years of age, SAEs occurred in 0.7% (11/1669) of the subjects in the QIV group, 0.7% (3/424) of the subjects in the 2010-2011 TIV group, and 1.0% (4/413) of the subjects in the investigational TIV group. Among the SAEs, 1 was considered (by the applicant) to be related to study vaccine and occurred in the 2010-2011 TIV group (febrile seizure 1 day post-vaccination). There were no deaths reported in the 3 years to < 9 years of age group.

Subgroup Analyses

Primary and secondary immunogenicity analyses by age groups (6 – <36 months and 3 – <9 years) were shown above. (Post hoc) subgroup analyses of immunogenicity by gender, race (Caucasian, Black, Hispanic, and all other), or study sites (69 investigators in US)

did not show any remarkable difference in immunogenic noninferiority of Fluzone Quadrivalent compared to Fluzone between the age groups, genders, race groups, or study sites.

Safety analyses on SAEs by age groups (6 – <36 months and 3 – <9 years) were shown above. (Post hoc) subgroup analyses of serious adverse events (SAE's) by gender, race (Caucasian, Black, Hispanic, and all other), or study sites (69 investigators in US) did not show any noteworthy difference in the distribution of SAEs between the age groups, genders, race groups, or study sites.

QIV03

This was a Phase III, randomized, active-controlled, 3-arm, multi-center study with planned enrollment of 675 subjects 65 years of age and older. The applicant included a 4th arm in this study to conduct an annual influenza vaccine study in healthy adults 18 to < 65 years of age for documenting the safety and immunogenicity of the licensed seasonal TIV vaccine [n=64 subjects (Group 4) are to be enrolled in this open-label cohort]. This review is restricted to the analyses comparing the three randomized arms, since the 4th group serves only as the applicant's annual influenza vaccine study.

The primary objective of this study was to demonstrate non-inferior immunogenicity of Fluzone Quadrivalent [QIV] compared to licensed 2010-2011 Fluzone (containing the primary B strain) [TIV1] and investigational Fluzone (containing the alternate B strain) [TIV2], as assessed by geometric mean titer (GMT) for each of the four virus strains separately among subjects ≥ 65 years of age.

Three treatment groups were as follows:
[TIV1] Licensed 2010-2011 Trivalent Influenza Vaccine (N=225 subjects planned)
[TIV2] Investigational Trivalent Influenza Vaccine (N=225 subjects planned)
[QIV] Investigational Quadrivalent Influenza Vaccine (N=225 subjects planned)

A total of 675 randomized subjects (225 subjects in each vaccine group) received one dose of study vaccine and were included in the Safety Analysis Set. The Per-Protocol Analysis Set included 220 subjects in the QIV group, 219 subjects in the 2010-2011 TIV group, and 221 subjects in the investigational TIV group.

Primary analysis of immunogenicity

The statistical criterion to show noninferior immune response to QIV compared to TIV was that the lower bound for each of the four 95% CIs for the GMT ratios (Fluzone Quadrivalent/Fluzone) be > 0.67. The comparators were subjects in the two Fluzone groups [TIV1 and TIV2] combined for A/H1N1 and A/H3N2 strains and subjects who received Fluzone with a matching B strain for the B/Brisbane and B/Florida strains.

The primary immunogenicity analyses were performed on the Per-Protocol population. The applicant performed the primary immunogenicity analyses as pre-specified, and the

applicant's results (Table 13) were verified by the reviewer. [Confidence intervals for the GMT ratios were calculated based on the normality assumption of log titers, and confidence intervals for the seroconversion rate differences were calculated based on the normal approximation to the binomial distribution.]

Table 13. Primary immunogenicity results: GMT ratio

Antigen strain	GMT ratio[QIV/TIV] (95% CI)	Non-inferiority of QIV to TIV (LB of CI of GMT ratio > 0.67)
H1N1	0.85 (0.67; 1.09)	Yes
H3N2	1.55 (1.25; 1.92)	Yes
B/Brisbane	1.27 (1.05; 1.55)	Yes
B/Florida	1.11 (0.90; 1.37)	Yes

* For B/Brisbane, GMT ratio of QIV/TIV1. For B/Florida, GMT ratio of QIV/TIV2

Secondary analysis of immunogenicity

The statistical criterion to show noninferior immune response to QIV compared to TIV was that the lower bound for each of the four 95% CIs for the seroconversion rate differences (Fluzone Quadrivalent - Fluzone) be > -10.0%. The comparators were subjects in the two Fluzone groups [TIV1 and TIV2] combined for A/H1N1 and A/H3N2 strains and subjects who received Fluzone with a matching B strain for the B/Brisbane and B/Florida strains.

Also for B/Brisbane and B/Florida strains, the statistical criterion to show higher immune response to QIV compared to TIV was that the lower bound for each of the two 95% CIs for the GMT ratios (Fluzone Quadrivalent/Fluzone) be > 1.5. The comparators were subjects who did not receive Fluzone with a matching B strain.

The secondary immunogenicity analyses were performed on Per-Protocol population. The applicant performed the secondary immunogenicity analyses as pre-specified, and the applicant's results (Tables 14 – 16) were verified by the reviewer:

Table 14. Secondary immunogenicity results: Seroconversion Rate (SCR) difference

Antigen strain	SCR(%) difference[QIV-TIV] (95% CI)	Non-inferiority of QIV to TIV (LB of CI of SCR difference > -10%)
H1N1	-3.86 (-11.50; 3.56)	No
H3N2	9.77 (1.96; 17.20)	Yes
B/Brisbane	9.91 (1.96; 17.70)	Yes
B/Florida	1.96 (-6.73; 10.60)	Yes

* For B/Brisbane, SCR difference of QIV-TIV1. For B/Florida, SCR difference of QIV-TIV2

Table 15. Secondary immunogenicity results: GMT ratio

Antigen strain	GMT ratio[QIV/TIV*] (95% CI)	Superiority of QIV to TIV (LB of CI of GMT ratio > 1.5)
B/Brisbane	1.75 (1.43; 2.14)	No
B/Florida	2.14 (1.74; 2.65)	Yes

* For B/Florida, GMT ratio of QIV/TIV1. For B/Brisbane, GMT ratio of QIV/TIV2

Table 16. Secondary immunogenicity results: Seroconversion Rate (SCR) difference

Antigen strain	SCR(%) difference[QIV-TIV*] (95% CI)	Superiority of QIV to TIV (LB of CI of SCR difference > 10%)
B/Brisbane	20.04 (12.90; 27.00)	Yes
B/Florida	24.05 (16.60; 31.20)	Yes

* For B/Florida, SCR difference of QIV-TIV1. For B/Brisbane, SCR difference of QIV-TIV2

Safety

A total of 3 subjects experienced an SAE. None of the SAEs occurred in the QIV group, and none was considered (by the applicant) related to vaccination. There were no deaths reported in this study.

Subgroup Analyses

(Post hoc) subgroup analyses of immunogenicity by gender, race (Caucasian and non-Caucasian), or study sites (12 sites in US) did not show any remarkable difference in immunogenic noninferiority of Fluzone Quadrivalent compared to Fluzone between the genders, race groups, or study sites.

(Post hoc) subgroup analyses of serious adverse events (SAE's) by gender, race, or study sites (12 sites in US) were not performed since there were only 3 subjects who experienced SAEs and none of the SAEs occurred in the QIV group.

Reviewer's Comments

1. For subjects 6 months to <9 years of age, noninferior immunogenicity of Fluzone Quadrivalent compared to Fluzone was shown for each of A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, based on the pre-specified noninferiority criteria [the lower bound for each of the four 95% CIs for the GMT ratios (Fluzone Quadrivalent/Fluzone) be > 0.67, and the lower bound for each of the four 95% CIs for the seroconversion rate differences (Fluzone Quadrivalent - Fluzone) be > -10.0%].

2. For subjects 65 years of age and older, noninferior immunogenicity of Fluzone Quadrivalent compared to Fluzone was shown for each of A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, based on the pre-specified noninferiority criterion [the lower bound for each of the four 95% CIs for the GMT ratios (Fluzone Quadrivalent/Fluzone) be > 0.67].

3. Numerical accuracy of the applicant's primary immunogenicity results and major safety results were verified by the reviewer.

4. No safety concerns were found.