

Application Type	BLA Supplement
STN	125510/191
CBER Received Date	April 28, 2020
PDUFA Goal Date	October 28, 2020
Division / Office	OVR
Committee Chair	Brenda Baldwin, PhD
Project Manager	Brenda Baldwin, PhD
Priority Review	No
Reviewer Name(s)	Zhong Gao, Ph.D. Mathematical Statistician
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Ph.D. Concurring Reviewer, Viral and Bioassay Team, VEB, DB, OBE
	Tsai-Lien Lin, Ph.D. Chief, Vaccine Evaluation Branch, DB, OBE
Applicant	Seqirus Inc.
(Proposed) Trade Name	FLUAD® Quadrivalent and FLUAD® (Trivalent)
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	15 mcg of hemagglutinin (HA) from each of the influenza strains included in the vaccine.
Dosage Form(s) and Route(s) of Administration	A sterile injectable emulsion supplied in 0.5 mL single-dose prefilled syringes. Intramuscular injection.
Dosing Regimen	A single 0.5 mL intramuscular injection in adults 65 years of age and older.
Indication(s) and Intended Population(s)	An inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and types B contained in the vaccine.
Purpose of Supplement	Change in labelling for both FLUAD Quadrivalent and FLUAD (Trivalent) in Section 8.4 Pediatric Use.

Table of Contents

1. Executive Summary 3

2. Regulatory Background 3

3. Sources of Data and Other Information Considered in the Review 3

 3.1 Review Strategy 3

 3.2 BLA/IND Documents That Serve as the Basis for the Statistical Review..... 3

4. Discussion of Individual Studies 4

 4.1 Study V118_05: A Phase III, Stratified, Randomized, Observer Blind, Controlled,
 Multicenter Clinical Study to Evaluate the Safety, Immunogenicity and Efficacy of an
 Adjuvanted Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-adjuvanted
 Comparator Influenza Vaccine in Children ≥ 6 to <72 Months of Age..... 4

 4.2 Study V70-29: A Phase III, Observer-Blind, Randomized, Multi-center Study to Evaluate the
 Safety, Tolerability, and Immunogenicity of Flud and Agriflu Compared to the Non
 Adjuvanted Trivalent Influenza Vaccine Fluzone in Children 6 to <72 Months of Age..... 7

5. Conclusions 8

 5.1 Statistical Issues and Collective Evidence 8

 5.2 Conclusions and Recommendations..... 9

1. EXECUTIVE SUMMARY

Seqirus Inc. submitted the revised US Package Inserts (USPIs) for both FLUAD Quadrivalent and FLUAD (Trivalent). The applicant updated the pediatric labelling text in Section 8.4 Pediatric Use. The proposed changes of labelling text are based on two Phase 3 studies V118-05 and V70-29 which were reviewed by CBER under BLA Supplement 125510/ [REDACTED]. The applicant concluded that the benefit of FLUAD Quadrivalent and FLUAD compared to non-adjuvanted influenza vaccines in children has not been established. Therefore, the applicant proposed that FLUAD Quadrivalent and FLUAD should not be approved for use in children. The Pediatric Review Committee (PeRC) reviewed and revised the proposed labelling text. I concur with the applicant's conclusion and recommend approval of this supplement.

2. REGULATORY BACKGROUND

Seqirus Inc. submitted the revised USPIs for both FLUAD Quadrivalent and FLUAD (Trivalent). The applicant updated the pediatric labelling text in Section 8.4 Pediatric Use. These proposed changes are based on CBER's review of BLA Supplement STN 125510/ [REDACTED]. This BLA Supplement included two Phase 3 studies entitled "A Phase III, Stratified, Randomized, Observer Blind, Controlled, Multicenter Clinical Study to Evaluate the Safety, Immunogenicity and Efficacy of an Adjuvanted Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-adjuvanted Comparator Influenza Vaccine in Children ≥ 6 to < 72 Months of Age" (Study V118-05) and "A Phase III, Observer-Blind, Randomized, Multi-center Study to Evaluate the Safety, Tolerability, and Immunogenicity of Fluad and Agriflu Compared to the Non Adjuvanted Trivalent Influenza Vaccine Fluzone in Children 6 to < 72 Months of Age" (Study V70-29). Dr. Charles (Yin Kiu) Cheung reviewed the statistical aspects of these two Phase 3 studies under STN125510/ [REDACTED]. The applicant and CBER agreed that the information from the studies should be included in the USPIs.

3. SOURCES OF DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

3.1 Review Strategy

The proposed changes of USPIs are based on CBER's review of STN 125510/ [REDACTED], which includes two Phase 3 studies. Statistical review of these studies was completed by Dr. Charles (Yin Kiu) Cheung during the review of STN 125510/ [REDACTED]. Therefore, this review focuses on the proposed changes on USPIs.

3.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following documents submitted to the BLA Supplement 125510/191 are reviewed:

- US Package Insert (USPI) for FLUAD Quadrivalent
- US Package Insert (USPI) for FLUAD (Trivalent)
- Clinical Study Report (CSR) of Study V118-05 (A Phase III, Stratified, Randomized, Observer Blind, Controlled, Multicenter Clinical Study to Evaluate the Safety, Immunogenicity and Efficacy of an Adjuvanted Quadrivalent Subunit

- Influenza Virus Vaccine Compared to Non-adjuvanted Comparator Influenza Vaccine in Children ≥ 6 to <72 Months of Age)
- CSR of Study V70-29 (A Phase III, Observer-Blind, Randomized, Multi-center Study to Evaluate the Safety, Tolerability, and Immunogenicity of Flud and Agriflu Compared to the Non Adjuvanted Trivalent Influenza Vaccine Fluzone in Children 6 to <72 Months of Age)

4. DISCUSSION OF INDIVIDUAL STUDIES

4.1 Study V118_05: A Phase III, Stratified, Randomized, Observer Blind, Controlled, Multicenter Clinical Study to Evaluate the Safety, Immunogenicity and Efficacy of an Adjuvanted Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-adjuvanted Comparator Influenza Vaccine in Children ≥ 6 to <72 Months of Age

This was a Phase 3 clinical study to evaluate the safety, immunogenicity and efficacy of FLUAD Quadrivalent, an adjuvanted quadrivalent subunit influenza vaccine (aQIV), compared to non-adjuvanted comparator influenza vaccine (Fluzone) in children ≥ 6 to <72 months of age. The study showed that aQIV was not able to meet the pre-specified efficacy success criteria to demonstrate relative efficacy of aQIV compared to a licensed seasonal influenza vaccine comparator (Fluzone). However, aQIV was found to be noninferior compared to the comparator vaccine based on immunogenicity endpoints. Both aQIV and the comparator vaccine were able to meet the CBER immunogenicity criteria in terms of the percentage of subjects with HI titers $>1:40$ and the percentage of subjects with seroconversion for all 4 strains contained in the vaccine.

The safety analyses showed that the percentages of subjects with local solicited adverse reactions were higher in the aQIV group when compared to the comparator vaccine (Table 1). The percentages of systemic solicited adverse reactions were overall higher in the aQIV group compared to the comparator group (Table 2). There were also higher percentages of subjects in the aQIV group who took prophylactic and therapeutic antipyretics/analgesics compared to the comparator group.

Table 1: Number (%) of Subjects with Any, Moderate and Severe Solicited Local Adverse Events Reported from 6 Hours Through Day 7 After Any Vaccination in Subjects ≥ 6 to < 72 Months of Age – Overall Period - Solicited Safety Set

Local Adverse Events	-	aQIV N=5138	Comparator ^a N=5056
Tenderness	n	5135	5053
-	Any	2218 (43.19%)	1711 (33.86%)
-	Moderate	602 (11.72%)	355 (7.03%)
-	Severe	83 (1.62%)	33 (0.65%)
Erythema	n	5134	5051
-	Any (≥ 1 mm)	1068 (20.80%)	869 (17.20%)
-	Moderate (26-50 mm)	154 (3.00%)	45 (0.89%)
-	Severe (>50 mm)	48 (0.93%)	26 (0.51%)
Induration	n	5134	5051
-	Any (≥ 1 mm)	732 (14.26%)	513 (10.16%)
-	Moderate (26-50mm)	142 (2.77%)	60 (1.19%)
-	Severe (>50 mm)	29 (0.56%)	10 (0.20%)
Ecchymosis	n	5134	5050
-	Any (≥ 1 mm)	396 (7.71%)	366 (7.25%)
-	Moderate (26-50mm)	23 (0.45%)	11 (0.22%)
-	Severe (>50 mm)	2 (0.04%)	1 (0.02%)

Source: Table 111 in the CSR of V118_05.

Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; n=number of subjects with solicited safety assessments at a particular time point; N=total number of subjects.

a. Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.

Table 2: Number (%) of Subjects with Any, Moderate and Severe Solicited Systemic Adverse Events Reported from 6 Hours through Day 7, After Any Vaccination in Subjects ≥ 6 to < 72 Months of Age – Overall Period - Solicited Safety Set

-	-	aQIV N=5138	Comparator^a N=5056
Systemic adverse events	-	n (%)	n (%)
Irritability	Any	1390 (27.07)	1138 (22.52)
-	Moderate	334 (6.50)	256 (5.07)
-	Severe	67 (1.30)	41 (0.81)
Sleepiness	Any	1348 (26.25)	1074 (21.25)
-	Moderate	269 (5.24)	182 (3.60)
-	Severe	39 (0.76)	19 (0.38)
Change in eating habits	Any	1157 (22.53)	884 (17.49)
-	Moderate	268 (5.22)	196 (3.88)
-	Severe	50 (0.97)	48 (0.95)
Diarrhea	Any	633 (12.33)	592 (11.72)
-	Moderate	120 (2.34)	125 (2.47)
-	Severe	36 (0.70)	27 (0.53)
Vomiting	Any	529 (10.30)	417 (8.25)
-	Moderate	116 (2.26)	84 (1.66)
-	Severe	18 (0.35)	12 (0.24)
Chills	Any	351 (6.84)	204 (4.04)
-	Moderate	71 (1.38)	25 (0.49)
-	Severe	9 (0.18)	6 (0.12)
Body temperature	-	-	-
Fever*	n	5121	5033
-	$\geq 38^{\circ}\text{C}$	983 (19.1%)	529 (10.5%)
-	$\geq 38.0^{\circ}\text{C} - < 39^{\circ}\text{C}$	749 (14.6%)	400 (7.9%)
-	$\geq 39^{\circ}\text{C} - < 40^{\circ}\text{C}$	212 (4.1%)	114 (2.3%)
-	$\geq 40^{\circ}\text{C}$	22 (0.4%)	15 (0.3%)
Other indicators of reactogenicity	-	-	-
Prophylactic use of antipyretics/analgesics	n	4843	4667
-	Yes	482 (9.95%)	318 (6.81%)
-	No	4361 (90.05%)	4349 (93.1%)
Therapeutic use of antipyretics/analgesics	n	4848	4670
-	Yes	1289 (26.59%)	712 (15.25%)
-	No	3559 (73.41%)	3958 (84.75%)

Source: Table 112 in the CSR of V118_05.

Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; n=number of subjects with solicited safety assessments at a particular time point; N=total number of subjects.

a. Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.

* Route overall (body temperature results are excluded if route of measurement is missing).

Fever was defined as body temperature $\geq 38^{\circ}\text{C}$ by any route.

Others include any use of antipyretics/analgesic for prevention or treatment of pain and/or fever.

In the USPI for FLUAD Quadrivalent, the applicant updated Section 8.4. Pediatric Use as follows:

“FLUAD QUADRIVALENT is not approved for use in children. In a clinical study with a safety population of 5339 children from 6 months through 5 years of age who received FLUAD QUADRIVALENT, tenderness (43.2%) was the most commonly reported ($\geq 10\%$) solicited local adverse reaction. The most commonly reported ($\geq 10\%$) systemic adverse reactions were irritability (27.1%), sleepiness (26.3%), change in eating habits (22.5%), fever (19.1%), diarrhea (12.3%) and vomiting (10.3%). The benefit of FLUAD QUADRIVALENT compared to non-adjuvanted influenza vaccine in children has not been established.”

4.2 Study V70-29: A Phase III, Observer-Blind, Randomized, Multi-center Study to Evaluate the Safety, Tolerability, and Immunogenicity of Fluad and Agriflu Compared to the Non Adjuvanted Trivalent Influenza Vaccine Fluzone in Children 6 to <72 Months of Age

This was a Phase 3 study to evaluate the safety, tolerability, and immunogenicity of FLUAD (Trivalent) and Agriflu compared to the non-adjuvanted trivalent influenza vaccine Fluzone in children 6 to <72 months of age. FLUAD met the pre-specified noninferiority criteria against Agriflu and Fluzone for all 3 strains contained in the vaccine in terms of seroconversion rates and Geometric Mean Titers (GMTs). FLUAD was not able to meet the prespecified criteria for the secondary endpoints of superiority against the comparator vaccines.

The safety analyses showed that the percentages of subjects with local solicited adverse reactions were higher in the FLUAD group when compared to the comparator vaccine groups (Table 3). The percentages of systemic solicited adverse reactions were overall higher in the FLUAD group compared to the comparator vaccine groups, too (Table 3).

Table 3: Summary of subjects with solicited adverse event reported from 6 hours through Day 7 after any vaccination (Solicited Safety Set)

Reaction	Fluad n/N (%)	Agriflu n/N (%)	Fluzone n/N (%)
Injection site	-	-	-
Ecchymosis	191/3075 (6%)	72/1450 (5%)	86/1446 (6%)
Ecchymosis PLT	2/3073 (<1%)	2/1450 (<1%)	3/1447 (<1%)
Erythema	312/3075 (10%)	109/1450 (8%)	101/1446 (7%)
Erythema PLT	2/3074 (<1%)	2/1450 (<1%)	0/1447 (0%)
Induration	258/3075 (8%)	62/1450 (4%)	67/1446 (5%)
Induration PLT	2/3072 (<1%)	0/1450 (0%)	1/1446 (<1%)
Tenderness	152/1495 (10%)	70/1025 (7%)	78/1012 (8%)
Swelling	217/3075 (7%)	34/1450 (2%)	43/1446 (3%)
Swelling PLT	0/3074 (0%)	0/1450 (0%)	1/1446 (<1%)
Pain	696/1580 (44%)	107/422 (25%)	111/429 (26%)
Systemic	-	-	-
Chills	154/1578 (10%)	23/423 (5%)	18/428 (4%)
Myalgia	216/1578 (14%)	43/423 (10%)	25/429 (6%)
Arthralgia	125/1578 (8%)	20/423 (5%)	16/429 (4%)
Headache	282/1578 (18%)	46/423 (11%)	38/429 (9%)
Fatigue	204/1578 (13%)	43/423 (10%)	31/430 (7%)
Eathabit	437/3076 (14%)	196/1450 (14%)	205/1446 (14%)
Diarrhea	423/3075 (14%)	231/1450 (16%)	220/1447 (15%)
Irritability	290/1496 (19%)	164/1024 (16%)	190/1013 (19%)
Crying	186/1463 (13%)	105/1001 (10%)	122/990 (12%)
Sleepiness	229/1495 (15%)	150/1024 (15%)	153/1012 (15%)
Vomiting	249/3075 (8%)	100/1451 (7%)	104/1446 (7%)
Fever ($\geq 38C$)	748/3074 (24%)	236/1450 (16%)	224/1446 (15%)

Source: adapted from Table 14.3.1.1.3.1.2 in CSR of V70-29.

n=number of subjects with solicited adverse event; *N*=total number of subjects with solicited safety assessment.

In the USPI for FLUAD (Trivalent), the applicant updated Section 8.4. Pediatric Use as follows:

“FLUAD is not approved for use in children. In a clinical study with a safety population of 3082 children from 6 months through 5 years of age who received FLUAD, injection site pain (44%) and tenderness (10%) were the most commonly reported local adverse reactions ($\geq 10\%$). The most commonly reported ($\geq 10\%$) systemic adverse reactions were fever (24%), irritability (19%), headache (18%), sleepiness (15%), change in eating habits (14%), diarrhea (14%), myalgia (14%), fatigue (13%), crying (13%) and chills (10%). The benefit of FLUAD compared to non-adjuvanted influenza vaccines in children has not been established.”

5. CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The applicant proposed changes to the USPIs for both FLUAD Quadrivalent and FLUAD (Trivalent). Based on the two Phase 3 studies V118-05 and V70-29, the applicant concluded that the benefit of FLUAD Quadrivalent and FLUAD compared to non-adjuvanted influenza vaccines in children has not been established. The Pediatric Review

Committee (PeRC) reviewed the proposed labelling text and decided to change to the following:

“Safety and effectiveness of FLUAD and FLUAD QUADRIVALENT (same manufacturing process and overlapping composition with FLUAD) were evaluated in clinical trials conducted in children 6 months to <72 months of age. Data from these trials are inconclusive to demonstrate the safety and effectiveness of FLUAD in children 6 months to <72 months of age. The safety and effectiveness of FLUAD in infants less than 6 months of age and in children older than 72 months of age have not been evaluated.”

5.2 Conclusions and Recommendations

The benefit of FLUAD Quadrivalent and FLUAD compared to non-adjuvanted influenza vaccines in children has not been established. The Pediatric Review Committee (PeRC) reviewed and revised the proposed labelling text. I concur with the applicant’s conclusion and recommend approval of this supplement.