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BLA Clinical Review Memorandum

Application Type	Supplemental BLA
STN	125297/118
CBER Received Date	02-Apr-2019
PDUFA Goal Date	31-Jan-2020
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Rachel Zhang MD
Review Completion Date / Stamped Date	16-Jan-2020
Supervisory Concurrence	Charu Mullick MD (Acting Team Leader) Douglas Pratt MD MPH (Acting Branch Chief)
Applicant	Seqirus
Established Name	Influenza Virus Vaccine
(Proposed) Trade Name	Agriflu
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each dose contains 15 µg of influenza hemagglutinin protein (45 µg total) from each of the following three influenza subtypes or lineages: • A/H1N1 • A/H3N2 • B Each dose may contain trace amounts of polysorbate, cetyltrimethylammonium bromide, formaldehyde, barium, egg proteins, kanamycin, and neomycin
Dosage Form(s) and Route(s) of Administration	Agriflu is supplied in a single-dose 0.5mL prefilled syringe to be administered by intramuscular injection
Dosing Regimen	Single 0.5 mL dose for intramuscular injection administered annually
Indication(s) and Intended Population(s)	Active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine in adults 18 years of age and older
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

AE	Adverse Event
AESI	Adverse Events of Special Interest
AR	Adverse Reaction
BARDA	Biomedical Advanced Research and Development Authority
BIMO	CBER Bioresearch Monitoring
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CFR	Code of Federal Regulations
CRF	Case Report Form
CSR	Clinical Study Report
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
GMTR	Geometric Mean Titer Ratio
GCP	Good Clinical Practice
HA	Hemagglutinin
HAI	Hemagglutination Inhibition Assay
HI	Hemagglutination Inhibition
IND	Investigational New Drug application
LL	Lower Limit
MPPS	Modified Per Protocol Set
NA	Neurominadase
OVRR	Office of Vaccines Research and Review
PeRC	Pediatric Review Committee
PI	Package Insert
PMC	Post marketing Commitment
PMR	Post marketing Requirement
PPS	Per Protocol Set
PREA	Pediatric Research Equity Act
QIV	Quadrivalent influenza vaccine
SAE	Serious Adverse Event
SP	Safety Population
sBLA	Supplemental Biologics License Application
SCR	Seroconversion Rate
SOC	System Organ Class
STN	Submission Tracking Number
TIV	Trivalent influenza vaccine
US	United States
WHO	World Health Organization

1. Executive Summary

Agriflu is an inactivated influenza vaccine containing purified surface antigens of influenza viruses type A and B, propagated in embryonated chicken eggs, and inactivated with formaldehyde. It is indicated for seasonal prophylaxis of influenza in individuals 18 years of age and older. This submission contains 3 clinical studies submitted by the applicant to satisfy two pediatric post-marketing requirements (Study V70_29 and V71_18) and one post-marketing commitment for a study in individuals 50 years of age and older (Study V71_22).

Study V70_29 was conducted in subjects 6 to <72 months of age. The study failed 2 out of the 6 primary immunogenicity endpoints to demonstrate the non-inferiority of Agriflu to a US-licensed comparator influenza vaccine in subjects 6 to <36 months of age. Study V71_18 was conducted in subjects 3 through 17 years. The study failed 3 out of the 6 primary immunogenicity endpoints to demonstrate the non-inferiority of Agriflu to a US-licensed comparator influenza vaccine in subjects 3 through 8 years of age. The safety profile of Agriflu in the entire pediatric age group was overall comparable to the control vaccine. Clinical disease endpoint efficacy was not evaluated in either of the two pediatric studies. Overall, studies V70_29 and V71_18 provided inconclusive evidence for the effectiveness of this vaccine in the pediatric population 6 months to <18 years of age. These studies do fulfill the pediatric post-marketing requirements, as stipulated in the Agriflu approval letter from November 2009.

Study V71_22 was a post-marketing commitment study in adults 50 years of age and older. The study failed to meet 4 out of the 6 primary immunogenicity objectives to demonstrate the non-inferiority of Agriflu to a US-licensed comparator vaccine. These results are of uncertain clinical significance given the lack of clinical disease endpoint efficacy data in this age group. As Agriflu is currently approved for this age group of individuals 50 years of age and older, there will continue to be language in the label to indicate that the immune response in the geriatric population is lower compared to younger adults.

2. Clinical and Regulatory Background

2.1 Previous Human Experience with the Product (Including Foreign Experience)

Agriflu was first approved for marketing in Italy in October 1986, under the trade name Agrippal. Agriflu was licensed in the US in November 2009. It is currently approved for marketing in 41 countries worldwide. Based on the most recent Periodic Safety Update Report covering through March 15, 2019, the cumulative worldwide exposure to Agriflu is estimated to be approximately 268,609,334 individuals.

2.2 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Agriflu was approved in the US on November 27, 2009 for adults 18 years of age and older under accelerated approval. At the time of approval, post-marketing requirements (PMR) and post-marketing commitments (PMC) were issued for a total of five studies.

Table 1: Summary of PMR/PMC in 2009 approval letter

PMC/ PMR #	Study # (Population)	Description	Submitted	STN

1	V58P13 (18-49 years)	Efficacy trial	2009-Dec-30	/001
2	V71_18 (3-17 years)	Non-inferiority immunogenicity and safety	2013-Feb-28	/046
3	V70_29 * (6-<36 months)	Safety and immunogenicity	2013-Jul-31 & 2013-Nov-19	/049
4	V71_25OB **	Pregnancy registry	Pending	--
5	V71_22 (≥50 years)	Non-inferiority immunogenicity and safety	2014-Sep-23 & 2015-Mar-12	/063

*Study V70_29, also designed to fulfill PMR #3, replaced Study V71_20 from original approval letter
**renumbered from V7125TP

Agriflu received traditional approval on October 29, 2010 based on review of data from study V58P13 which satisfied PMR #1. In 2016, the applicant was notified that the final study reports of the three completed studies, V71_18, V70_29 and V71_22 (PMR #2, 3, 5) along with a revised label should be submitted to fulfill these post-approval commitments. The final study reports from V71_18, V70_29 and V71_22 and proposed labeling changes were submitted in April 2019 in the current efficacy supplement.

Current US marketing status
Agriflu is not currently marketed in the US. (b) (4) . The currently available supply is only for the trivalent formulation; and the applicant does not plan to manufacture a quadrivalent formulation of this product. In further communications with the applicant, the applicant indicated an interest in maintaining an active file for Agriflu ((b) (4) because of a manufacturing contract with Biomedical Advanced Research and Development Authority (BARDA).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

No Bioresearch Monitoring auditing was done for any of the clinical sites in this supplement. Good Clinical Practices (GCP) and data integrity issues were noted by the applicant for study V71_18, which are discussed under Section 6.2.

3.3 Financial Disclosures

Covered clinical study (name and/or number): V70_29, V71_18, V71_22		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 327		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: $(b) (4) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

4. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

4.1 Review Strategy

This review is a high-level, abbreviated review given the product will not be marketed in the US. Each of the pediatric PMR studies (V70_29, V71_18) and the PMC study (V71_22) are reviewed separately in Section 5. For each study, the pertinent immunogenicity and safety results are presented, and the findings are discussed from the perspective of labeling changes warranted based on the study findings. Additionally, the determination regarding fulfillment of the associated PMR/PMCs is discussed in this review.

4.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following files served as the basis for this clinical review:
STN 125297/118 modules 1.14 Labeling, 1.3.4 Financial Certification and Disclosure, 5 Clinical Study Reports.

4.3 Table of Studies/Clinical Trials

Table 2: Summary of Studies Included in this Supplement

Study	Study Design	Control	Number of Subjects	Age Range	Countries
V70_29	Phase 3, randomized, active controlled, observer-blind	Fluzone	1843	6-<72 months	Argentina, Australia, Chile, Philippines, South Africa
V71_18	Phase 3 randomized, active controlled, observer-blind	Fluzone (3-<4 years) Fluvirin (4-17 years)	2804	3-17 years	Mexico, Colombia, Panama, Philippines

V71_22	Phase 4, randomized, active controlled, observer-blind	Fluvirin	2902	50 years and older	Czech Republic, Philippines, South Africa, Thailand

5. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

5.1 Study V70_29

Study V70_29 was a Phase 3 safety and immunogenicity study comparing Agriflu and Fluad, a MF59-adjuvanted trivalent influenza vaccine, to Fluzone, a US-licensed vaccine, in healthy children 6 months to <72 months of age.

5.1.1 Objectives

The primary immunogenicity objective was to demonstrate the non-inferiority of two doses of Agriflu to Fluzone for all three vaccine strains, in subjects 6 months to <36 months of age, 21 days after the last vaccination, as measured by:

- Differences in percentages of subjects achieving seroconversion, defined as a pre-vaccination titer < 1:10 and a post-vaccination hemagglutination inhibition (HI) titer ≥ 1:40 *or* as a pre-vaccination titer ≥ 1:10 and a minimum four-fold rise in post-vaccination antibody titer and,
- Ratio of post-vaccination geometric mean titers (GMT).

Secondary immunogenicity objectives were to evaluate the immunogenicity of Agriflu in terms of percentage of subjects with post-vaccination HI titer ≥1:40, seroconversion rates and GMTs as well as GMT ratios, as measured by the HI assay on study day 29, day 50, and day 209.

Safety objectives include evaluation of the safety and tolerability for 7 days after each vaccine dose, assessment of unsolicited AEs until day 50, and assessment of serious adverse events (SAEs), AEs of special interest (AESI), AEs leading to withdrawal from the study, and new onset of chronic disease through day 394.

Reviewer comment: Although this study enrolled subjects 6 to <72 months of age, the primary immunogenicity analysis for Agriflu only included subjects 6 to <36 months of age to address the age requirements specified in PMR #3 issued in the Agriflu approval letter. Of note, this study was also designed as a study to support immunogenicity of Fluad; and included multiple separate primary and secondary endpoints specific to Fluad analyses. The current review focuses on objectives, analysis and findings pertinent to Agriflu.

5.1.2 Design Overview

Study subjects were randomized to receive Fluad, Agriflu, or Fluzone and stratified by age and study center. Subjects 6 to <36 months of age were randomized to Fluad, Agriflu, or Fluzone in a 3:2:2 ratio. Subjects 36 to <72 months of age were randomized to Fluad, Agriflu or Fluzone in a 4:1:1 ratio.

Subjects aged 6 to <36 months received two 0.25 mL study vaccinations, while subjects 36 to <72 months received two 0.5 mL study vaccinations. Study vaccines were

administered intramuscularly on Days 1 and 29. Subjects were followed to Day 394 in this study.

Blood samples for immunogenicity assessments were collected in a subset of 2500 subjects, pre-vaccination on Days 1 and 29, on Day 50 (i.e., 21 days after the second vaccine dose), and on Day 180.

Safety was assessed by collection of information on solicited AEs for seven days post-vaccination; on unsolicited AEs until Day 50; and SAEs, new onset chronic diseases, and AEs leading to premature study withdrawal for the entire study period. Information on AESIs was collected at the study visits on Days 29 and 50 and during monthly telephone calls conducted from Day 80 to Day 360. Safety laboratory monitoring (hemoglobin, white blood cell count, platelet count, ALT, AST, and creatinine) was performed on Days 1 and 8 in a subset of 200 subjects.

The study was conducted at 32 centers in five countries: Argentina, Australia, Chile, the Philippines, and South Africa.

5.1.3 Study Treatments or Agents Mandated by the Protocol

Agriflu 2011 SH formulation
A 0.5 or 0.25mL dose of Agriflu contains purified viral envelope-glycoproteins Neuraminidase (NA) and HA recommended for inclusion in the vaccine composition for the 2011 influenza season in the Southern Hemisphere.
Lot numbers: B51D04N1, B51D04N1A, B51D04N1B

Fluad 2011 SH formulation
A 0.5 or 0.25ml dose of Fluad contains purified viral envelope-glycoproteins NA and HA recommended for the 2011 influenza season in the Southern Hemisphere.
Lot numbers: A52P14H1A, A52P15H1A, A52P16H1A, B52D21N1, B52D21N1A, B52D21N1B

Fluzone 2011 SH formulation
A 0.5 or 0.25mL dose of Fluzone contains viral envelope-glycoproteins NA and HA recommended for the 2011 influenza season in the Southern Hemisphere.
Lot numbers: U3792BA, U3641BA

5.1.4 Surveillance/Monitoring

Table 3:. Monitoring and surveillance procedures for study V70_29

Study Day	Day 1	Day 8	Day 29	Day 36	Day 50	Day 80, 110, 140, 170, 250, 270, 300, 330, 360	Day 209	Day 394
Procedures performed	-ICF -Eligibility -Medical history -Physical examination -Serology blood draw -Safety labs -Study vaccine -Dispense diary card #1	-Safety labs -Diary card #1 reviewed -Assess local/systemic reactions -Assess all AEs -Assess SAEs, NOCD, and AEs leading to study termination	-Physical examination -Serology blood draw -Study vaccine -Dispense diary card #2 -Diary card #1 collected and reviewed -Assess local/systemic reactions	-Diary card #2 reviewed -Assess local/systemic reactions -Assess all AEs -Assess SAEs, NOCD, and AEs leading to study termination -Concomitant medication	-Physical examination -Serology blood draw -Diary card #2 collected and reviewed -Memory aid dispensed -Assess all AEs -Assess SAEs, NOCD, and AEs	-Assess SAEs, NOCD, and AEs leading to study termination -Assess AESIs -Concomitant medications	-Physical examination -Serology blood draw -Memory aid reviewed -Assess SAEs, NOCD, and AEs leading to study termination	-Memory aid reviewed -Assess SAEs, NOCD, and AEs leading to study termination -Concomitant medications -Study termination

	-Assess local/systemic reactions -Assess all AEs -Assess SAEs, NOCD, and AEs leading to study termination -Concomitant medications	-Concomitant medication	-Assess all AEs -Assess SAEs, NOCD, and AEs leading to study termination -Concomitant medications		leading to study termination -Assess AESIs -Concomitant medications		-Concomitant medications	

Source: Adapted from sBLA 125297/118; Clinical Study Report V70_29 Section 9.5.1, Table 9.5.1-1

5.1.5 Endpoints and Criteria for Study Success

The primary objective was to demonstrate the non-inferiority of Agriflu to Fluzone as measured by the difference in seroconversion rates and the GMT ratio in subjects 6 months to <36 months of age. Non-inferiority would be demonstrated if the lower bound of the two-sided 97.4% confidence interval (CI) for the difference in seroconversion rates was greater than -10 percentage points and if the lower bound of the two-sided 97.4% CI for the GMT ratio was greater than 0.667 for each of the three vaccine strains.

Reviewer comment: Since the study was also designed to study the immunogenicity of Fluad, the alpha for the non-inferiority analysis was split so that the confidence interval used in the definition for success criteria was 97.4% instead of the usual 95%. These pre-specified success criteria, which were agreed upon with CBER, are acceptable

5.1.6 Statistical Considerations & Statistical Analysis Plan

Please refer to the statistical review for a detailed description of statistical analysis.

5.1.7 Study Population and Disposition

5.1.7.1 Populations Enrolled/Analyzed

All Enrolled Population: All subjects who had signed an informed consent, undergone screening procedures and were assigned randomly to one of the study vaccine groups

Full Analysis Set (FAS): All subjects in the enrolled population who received a study vaccination and provided at least one evaluable serum sample before and after vaccination

Per Protocol Set (PPS): All subjects in the FAS immunogenicity population who correctly received the vaccine, provided evaluable serum samples at the relevant time points, and had no major protocol violation, as defined, prior to unblinding

Safety Population (SP): All subjects who had received at least one study vaccine and had postvaccination safety data

5.1.7.1.1 Demographics

A total of 6104 subjects were enrolled, and 6078 subjects were vaccinated in this study. Of the vaccinated subjects, 1478 were in the Agriflu arm, 3125 in the Fluad arm, and 1474 in the Fluzone arm. Key demographic and baseline characteristics are shown in the following table.

Table 4: Demographic Characteristics of Subjects in the all enrolled set for study V70_29

	6 -<36 Months	6 -<36 Months	6 -<36 Months	6-<72 Months	6-<72 Months	6-<72 Months
	Agriflu N=1050	Fluad N=1525	Fluzone N=1040	Agriflu N=1486	Fluad N=3136	Fluzone N=1478
Mean Age (Months)	21.1	20.8	20.9	30.2	37.1	30.0
% Male	51%	49%	50%	51%	51%	50%
Asian	82%	83%	82%	76%	72%	76%
Black	10%	10%	10%	13%	14%	13%
Caucasian	5%	5%	5%	7%	9%	7%
Hispanic	3%	2%	3%	4%	4%	5%
Other	<1%	<1%	0	<1%	<1%	0
Previously vaccinated against Influenza	0	<1%	<1%	0	<1%	<1%

Source: Adapted from sBLA 125297/118; Clinical Study Report V70_29 Section 11.2, Table 11.2-1

Key demographic characteristics were similar across the treatment arms in the 6 to <36 months age subgroup. Regarding previous vaccination against influenza, no subjects in the Agriflu arm were previously vaccinated, and a very small proportion of subjects in the comparator Fluzone arm (<1%) were previously vaccinated.

Reviewer comment: Because this study was conducted outside the US, the distribution by race and ethnicity is less reflective of the demographics prevalent within the US. However, the results from this study population are considered applicable to a similar influenza vaccine-naïve pediatric population in the US.

5.1.7.1.2 Subject Disposition

The percentage of subjects who prematurely discontinued the study was 6% or less in each arm and balanced among the arms.

5.1.8 Efficacy Analyses

5.1.8.1 Analyses of Primary Endpoint(s)

Table 5: Results for Primary Endpoint–Non-Inferiority Analysis Comparing Agriflu to Fluzone in Subjects Aged 6 to <36 Months (PPS)

Seroconversion Rate	**Agriflu N=642**	**Fluzone N=635**	**Difference (97.4% CI)**
A/H1N1	78.8%	84.1%	-5.5% (-10.13, 0.47)
A/H3N2	89.9%	92.6%	-2.84% (**-6.16**, 0.5)
B	82.7%	85.5%	-2.49% (**-7.01**, 2.0)
Geometric Mean Titers (GMTs) on Day 50	**Agriflu N=642**	**Fluzone N=635**	**GMT Ratio (97.4% CI)**
A/H1N1	370	487	0.76 (0.62, 0.93)
A/H3N2	698	912	0.77 (**0.68**, 0.86)
B	144	152	0.94 (**0.8**, 1.11)

Source: Adapted from sBLA 125297/118; Clinical Study Report V70_29, Section 11.4.1.1.2, Tables 11.41.1.2-1 and 11.4.1.1.2-2

Bolded text denotes parameters for which the noninferiority criteria were met

As shown above, the criteria for demonstration of non-inferiority were met for 4 of the 6 immunogenicity endpoints. The seroconversion and GMT ratio endpoints were not met for the A/H1N1 strain.

Reviewer comment: The two endpoints for A/H1N1 were extremely close to the prespecified criteria (-10.13 instead of -10 for seroconversion, and 0.62 instead of 0.667 for GMT ratio).

5.1.8.2 Analyses of Secondary Endpoints

Immunogenicity results for the percentage of subjects with HI titer >1:40 and percentage of subjects with seroconversion for Agriflu, Fluad, and Fluzone are shown in the table below.

Table 6: Results for Secondary Immunogenicity Objective—Seroconversion Rate and Percentage of Subjects with Post-Vaccination HI Titer ≥1:40 in Subjects 6 to <72 Months (FAS)

Seroconversion Rates (95% CI)	**Agriflu N=765**	**Fluad N=680**	**Fluzone N=757**
A/H1N1	79.4 (76.3, 82.2)	92.9% (90.8, 94.8)	84.5% (81.8, 87.1)
A/H3N2	89.4% (87.0, 91.5)	96.5% (94.8, 97.7)	92.3% (90.2, 94.1)
B	84.6% (81.8, 87.1)	98.0% (96.6, 98.9)	86.0% (83.3, 88.4)
Percentage of Subjects with Post-Vaccination HI Titer > 1:40 (95% CI)	**Agriflu N=765**	**Fluad N=680**	**Fluzone N=757**
A/H1N1	88% (85.6, 90.1)	99.3% (98.4, 99.8)	91.2% (89.0, 93.0)
A/H3N2	99.4% (98.6, 99.8)	99.7% (99.0, 99.97)	99.5% (98.8, 99.9)
B	86.3% (83.8, 88.6)	98.8% (97.55, 99.4)	88.8% (86.5, 90.85)

Source: Adapted from sBLA 125297/118; Clinical Study Report V70_29, Tables 11.4.1.1.1-2, 11.4.1.2.6-1, 11.4.1.2.6-3

Reviewer comment: Both the percentage of subjects with post-vaccination HI titer ≥1:40 and seroconversion rates were slightly lower for the Agriflu group compared to Fluzone or Fluad, most notably for A/H1N1. The lower response for A/H1N1 is not unexpected given the failed endpoints for this strain in the primary immunogenicity analysis.

5.1.9 Safety Analyses

5.1.9.1 Overview of Adverse Events

Table 7: Percentage of subjects with adverse reactions and with adverse events after any vaccination (SP)

	6-<36 Months	6-<36 Months	6-<36 Months	6-<72 Months	6-<72 Months	6-<72 Months
	Agriflu N=1028	Fluad N=1498	Fluzone N=1015	Agriflu N=1453	Fluad N=3082	Fluzone N=1451
Any solicited AR	50%	58%	53%	51%	62%	51%
Any solicited local AR	15%	19%	17%	20%	35%	21%
Any solicited general AR	43%	48%	43%	42%	48%	39%
Any unsolicited AE	60%	58%	61%	55%	49%	58%

Any AE leading to premature study discontinuation	<1%	0	<1%	<1%	<1%	<1%
Any AESI	0	<1%	0	0	<1%	0
Any new onset chronic disease	2%	2%	3%	2%	2%	2%
Any SAE	5%	5%	5%	5%	4%	4%

Source: Adapted from sBLA 125297/118; Clinical Study Report V70_29, Tables 12.2.1-1 and 12.2.1-3

As shown in the table above, the percentages of adverse events (AE) and adverse reactions (AR) were similar for all three vaccine arms in both age groups, except, for the increase in solicited adverse reactions reported for the Fluad arm all cohorts.

The percentages of subjects with each individual local solicited adverse reaction after the first and second study vaccination are shown in the following table.

Table 8: Percentage of subjects with individual local solicited adverse reactions after each vaccination (SP)

	6-<36 Months	6-<36 Months	6-<36 Months	6-<72 Months	6-<72 Months	6-<72 Months
	Agriflu N=1025	Fluad N=1494	Fluzone N=1010	Agriflu N=1430	Fluad N=2991	Fluzone N=1422
First vaccination						
Ecchymosis	3%	3%	4%	3%	4%	4%
Erythema	5%	5%	5%	5%	6%	5%
Induration	3%	3%	2%	3%	5%	3%
Swelling	1%	2%	1%	2%	3%	2%
Tenderness	6%	8%	7%	-	-	-
Pain	-	-	-	17%	33%	20%
Second vaccination						
Ecchymosis	1%	3%	2%	2%	3%	3%
Erythema	3%	5%	2%	4%	6%	3%
Induration	1%	2%	2%	2%	5%	2%
Swelling	<1%	2%	1%	1%	5%	1%
Tenderness	3%	5%	3%	-	-	-
Pain	-	-	-	15%	28%	16%

Source: Adapted from sBLA 125297/118; Clinical Study Report V70_29, Tables 12.2.3.1-1

The percentages of subjects with each individual local solicited adverse reaction were low (<10%) except for pain. The percentages of subjects with individual solicited local adverse reactions were either the same or higher in the Fluad arm compared to the two unadjuvanted vaccine arms.

The percentages of subjects with solicited generalized adverse reaction are shown in the following table.

Table 9: Percentage of subjects with individual generalized solicited adverse reactions after vaccination (SP)

	6-<36 Months	6-<36 Months	6-<36 Months	6-<72 Months	6-<72 Months	6-<72 Months
	Agriflu N=1025	Fluad N=1494	Fluzone N=1010	Agriflu N=1430	Fluad N=2991	Fluzone N=1422
First vaccination						

Any irritability	12%	14%	13%	-	-	-
Any crying	7%	10%	9%	-	-	-
Any sleepiness	12%	12%	12%	-	-	-
Any change in eating habits	10%	11%	10%	9%	11%	10%
Any diarrhea	12%	13%	14%	11%	10%	11%
Any vomiting	4%	6%	6%	4%	6%	5%
Fever	9%	13%	10%	8%	15%	9%
Temperature >40° C	<1%	<1%	<1%	<1%	<1%	<1%
Chills	-	-	-	2%	7%	2%
Myalgia	-	-	-	5%	10%	4%
Arthralgia	-	-	-	2%	5%	2%
Headache	-	-	-	6%	13%	6%
Fatigue	-	-	-	7%	10%	5%
Second vaccination						
Any irritability	7%	9%	8%	-	-	-
Any crying	5%	5%	6%	-	-	-
Any sleepiness	6%	6%	6%	-	-	-
Any change in eating habits	6%	6%	7%	6%	6%	7%
Any diarrhea	10%	9%	8%	8%	6%	7%
Any vomiting	3%	3%	3%	3%	3%	3%
Fever	9%	13%	9%	9%	14%	8%
Temperature >40° C	<1%	0	<1%	<1%	0	<1%
Chills	-	-	-	4%	5%	2%
Myalgia	-	-	-	6%	7%	4%
Arthralgia	-	-	-	3%	4%	3%
Headache	-	-	-	6%	8%	5%
Fatigue	-	-	-	5%	6%	4%

Source: Adapted from sBLA 125297/118; Clinical Study Report V70_29, Tables 12.2.3.1-2, 12.2.3.1-4

The percentage of subjects with generalized solicited adverse reaction were similar in the Agriflu and Fluzone arms and similar or higher in the Fluad arms, most notably in the percentage of subjects with fever after vaccination.

Reviewer comment: The proportions of subjects who experienced solicited adverse reactions were comparable in the Agriflu and Fluzone arms. Of note, Fluad, an adjuvanted vaccine, appears to be more reactogenic compared to the two unadjuvanted vaccines, Agriflu and Fluzone.

Unsolicited Adverse Events

The percentages of subjects reporting at least one unsolicited AE were similar among the three groups (55% in the Agriflu group, 49% in the Fluad group, 58% in the Fluzone group). The most commonly reported unsolicited AEs in the 6 to <36 months age group, were upper respiratory tract infection (19-20% of subjects in the three vaccine arms), nasopharyngitis (11-13% of subjects in the three arms), and gastroenteritis (6-7% of subjects in the three arms). The most commonly reported unsolicited AEs in the total study population of 6 to <72 months were upper respiratory tract infection (14-17% of subjects in the three vaccine arms), nasopharyngitis (9-12% of subjects in the three arms), and gastroenteritis (4-6% of subjects in the three arms).

5.1.9.2 Deaths

There were 8 deaths reported during study participation: 4 in the Agriflu arm (closed head injury, pneumonia with severe asthma exacerbation, disseminated intravascular coagulopathy, acute gastroenteritis with severe dehydration), 1 in the Fluad arm (septic shock), and 3 in the Fluzone arm (drowning, sepsis, dehydration). According to the investigators, none of the deaths were related to the study vaccine.

Reviewer comment: Narratives of deaths were reviewed and none of the deaths appear temporally or causally related to the study vaccines.

5.1.9.3 Nonfatal Serious Adverse Events

Serious adverse events were reported in 5% of subjects in the Agriflu arm and 4% of subjects in the Fluad and 4% in the Fluzone arm. The most commonly reported SAEs were in the system organ class, infections and infestations. Among SAEs reported in the study, only one SAE, an event of type III hypersensitivity reaction in the Fluad arm, was judged by the investigator to be possibly related to study vaccine; and the remaining SAEs were judged by the investigators to be unrelated to the study vaccine.

5.1.9.4 Adverse Events of Special Interest (AESI)

There was no AESI reported in the Agriflu arm.

5.1.9.5 Clinical Test Results

No clinical laboratory abnormalities were reported as adverse events.

5.1.9.6 Dropouts and/or Discontinuations

Ten subjects discontinued prematurely from the study because of an adverse event. This includes the eight deaths previously discussed. The additional two subjects were both in the Fluad arm and withdrew due to varicella (on Day 24) and hydronephrosis (Day 249).

5.1.10 Study Summary and Conclusions

In this safety and immunogenicity study in subjects 6 to <36 months, Agriflu marginally missed 2 of the 6 prespecified immunogenicity endpoints, both for A/H1N1, for noninferiority against a licensed influenza control vaccine. It is uncertain whether such a narrow miss would translate to a significant difference in vaccine efficacy in the clinical setting. Based on these immunogenicity results alone, there is insufficient evidence to conclude that the vaccine is ineffective. At the same time, without a clinical endpoint efficacy study, there is also inconclusive evidence that this vaccine will be effective in this age group, given the failed endpoints. Safety was overall comparable between Agriflu and the licensed comparator vaccine, and no safety signal was observed in the study to suggest that Agriflu would be unsafe in this pediatric population.

5.2 Study V71_18

Study V71_18 was a Phase 3 safety and immunogenicity study comparing Agriflu to a US-licensed comparator influenza vaccine in healthy children 3 to 17 years of age.

5.2.1 Objectives

The primary objective of the study was to demonstrate the non-inferiority of the HI antibody responses for the three influenza vaccine strains contained in the Agriflu vaccine compared to US-licensed compared vaccine controls in subjects 3 through 8 years of age 21 days after the last vaccination as measured by:

- Differences in percentages of subjects achieving seroconversion, defined as a pre-vaccination titer <1:10 and a post-vaccination HI titer ≥ 1:40 or as a pre-vaccination titer ≥ 1:10 and a minimum four-fold rise in post-vaccination antibody titer and
- Ratio of post vaccination GMT.

The secondary immunogenicity objective was to evaluate the immunogenicity of Agriflu and the control vaccine for the three influenza strains 21 days after last vaccination as measured according to the criteria for demonstration of immunogenicity of seasonal influenza vaccines in adults for accelerated approval (FDA Guidance for Industry, Clinical Data Needed to Support the Licensure of Seasonal Influenza Vaccines). The safety objective was to evaluate safety and tolerability of Agriflu and the control vaccines.

5.2.2 Design Overview

Study subjects were randomized in a 2:1 ratio to receive either Agriflu or the control vaccine. Fluvirin was the control vaccine for subjects 4 years of age through 17 years. Since Fluvirin is not licensed for use in children younger than 4 years of age in the U.S., Fluzone was used as the control vaccine in subjects 3 to <4 years of age in the study.

Subjects 3 through 8 years of age who were influenza vaccine-naïve received two doses of study vaccine administered four weeks apart. Subjects 3 to 8 years of age, who had previously received two doses of a licensed influenza vaccine in a single influenza season, received a single dose of study vaccine. All subjects 9 years of age and older received a single dose of study vaccine. Immunogenicity was assessed in subjects 3 through 8 years of age only. Blood for antibody response was obtained pre-vaccination and 21 days after the last study vaccination. Safety was followed for six months from the last vaccination.

5.2.3 Population

The study population consisted of healthy children and adolescents, ages 3 through 17 years, who had not had influenza vaccine or documented or suspected influenza disease within the past 6 months.

5.2.4 Study Treatments or Agents Mandated by the Protocol

<u>Agriflu</u>
A 0.5 mL dose of each vaccine contains purified NA and HA glycoproteins [including 15 µg of HA for each influenza strain: A/H1N1, A/H3N2, and B].
Lot #: 107001B.

<u>Fluvirin</u>
A 0.5 mL dose of each vaccine contains purified NA and HA glycoproteins [including 15 µg of HA for each influenza strain: A/H1N1, A/H3N2, and B].
Lot #: 11162401A

Fluzone
A 0.5 mL dose of each vaccine contains purified NA and HA glycoproteins [including 15 µg of HA for each influenza strain: A/H1N1, A/H3N2, and B].
Lot #: U3564AA

5.2.5 Sites and Centers

The study was conducted in 13 centers across 4 countries: Mexico, Colombia, Panama and Philippines.

5.2.6 Surveillance/Monitoring

Table 10. Monitoring and surveillance procedures for study V71_18

Study Day	Day 1 (all)	Day 8 (all)	Day 22 (vaccine non-naïve only)	Day 29 (vaccine naïve only)	Day 36 (vaccine naïve only)	Day 50 (vaccine naïve only)	Day 180 (vaccine non-naïve only)	Day 209 (vaccine naïve only)
Procedures performed	-ICF -Eligibility -Medical history -Physical examination -Urine pregnancy test -Serology blood draw -Study vaccine -Dispense diary card -Assess local/systemic reac ions -Assess AEs -Concomitant medications	-Diary card reviewed -Assess local/systemic reactions -Assess all AEs -Concomitant medication	-Urine pregnancy test -Physical examination -Serology blood draw -Dispense memory aid -Diary card reviewed -Assess AEs -Concomitant medications	-Eligibility -Physical examina ion -Serology blood draw -Study vaccine -Diary card #2 dispensed -Diary card #1 reviewed -Assess local/systemic reactions -Assess AEs -Concomitant medication	-Assess local/systemic reactions -Assess AEs -Concomitant medications	-Physical examination -Serology blood draw -Memory aid dispensed -Diary card #2 reviewed -Assess AEs -Concomitant medications	-Memory aid reviewed -Assess AEs -Concomitant medications -Study termination	-Memory aid reviewed -Assess AEs -Concomitant medications -Study termination

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_18, Table 2-11, 2-12

5.2.7 Endpoints and Criteria for Study Success

Non-inferiority of Agriflu to the licensed comparator influenza vaccine was demonstrated if the upper bound of the two-sided 95% CI of the ratio of the GMTs ($GMT_{control}$/$GMT_{Agriflu}$) at 21 days after last vaccination does not exceed 1.5, AND the upper bound of the two-sided 95% CI of the difference between the seroconversion rates ($Seroconversion_{control}$ – $Seroconversion_{Agriflu}$) at 21 days after last vaccination does not exceed 10 percentage points.

Reviewer comment: These success criteria for the primary immunogenicity endpoints are reasonable for demonstration of non-inferiority for influenza vaccines.

5.2.8 Statistical Considerations & Statistical Analysis Plan

See statistical review for detailed description of statistical analysis.

5.2.9 Study Population and Disposition

5.2.9.1 Populations Enrolled/Analyzed

Exposed Population: all subjects in the enrolled population who received at least one study vaccination

Immunogenicity Full Analysis Set (FAS): all subjects in the enrolled population who received at least one study vaccination and provided at least one evaluable serum sample

Immunogenicity Per Protocol Set (PPS): all subjects who correctly received all study vaccinations, provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding

Safety Population (SP): all subjects in the Exposed Population who provided post vaccination safety data

5.2.9.1.1 Demographics

Table 11: Demographic Characteristics of Subjects – All Enrolled Subjects

	3 through 8 Years	3 through 8 Years	3 through 8 Years	9 through 17 Years	9 through 17 Years	9 through 17 Years
	Agriflu N=1042	Control N=533	Total N=1575	Agriflu N=817	Control N=412	Total N=1229
Mean Age (Years)	5.6	5.6	5.6	12.4	12.3	12.4
% Male	50%	50%	50%	51%	48%	50%
Asian	71%	70%	71%	79%	79%	79%
Black	<1%	<1%	<1%	0	0	0
Hispanic	28%	29%	29%	21%	21%	21%
Pacific/Hawaii	<1%	0	<1%	0	0	0
Vaccine Naïve	88%	86%	87%	0	0	0

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_18 Table 11.2-1

Reviewer comment: The ethnicity/race profile reflect populations at the sites where the study was conducted. Overall, the treatment arms were balanced with respect to the ethnicity and/or race. In the 3 through 8 years old subgroup, the majority of subjects were influenza vaccine-naïve, which likely differs from the US population with higher vaccination uptake rates. This may impact the applicability of some of the immunogenicity results to the U.S. population in this age group. There were no vaccine-naïve subjects in the older cohort of children ages 9 through 17 years.

5.2.9.1.2 Subject Disposition

In the 3 through 8 years group, 98% of all enrolled subjects in the Agriflu group, 92% in the Fluvirin group, and 92% in the Fluzone group completed the study. In the 9 through 17 years age group, 99% of all enrolled subjects in the Agriflu group and 99% of subjects in the Fluvirin group completed the study.

During routine monitoring of the study sites, concerns were raised about GCP violations at one site in Mexico (Site 10; enrolled 312 subjects). An audit of this site was conducted by the applicant from 11 May 2011 through 13 May 2011 which confirmed instances of serious GCP noncompliance including multiple instances of protocol noncompliance and early unblinding. Data from this site was excluded from the primary analyses. Given the findings at this site, the applicant decided to re-monitor and comprehensively review information at all V71_18 study sites.

Noncompliance with GCP was identified at 11 of the 12 study sites. The issues with study conduct are described by category.

- Informed consent: Overall, there were 3860 irregularities noted related to procedures of the informed consent process (64% of subjects) and 5906 findings related to poor documentation of the informed consent process (69% of subjects).

- Source Documentation: Deviations in GCP for source documentation were reported at 9 study sites. Example deviations include instances such as symptoms dairy completed by study personnel on the same day or no documented phone calls made to solicit adverse reactions. It is not possible to determine how many subjects were impacted at a given site.

- Protocol Noncompliance: Deviations related to protocol noncompliance were reported at 9 sites. Most notable deviation was the finding of missing medical or vaccination history in 352 subjects (13% of all enrolled subjects).

To address the major violations, a re-analysis of the immunogenicity data was performed using a modified per protocol set (MPPS) which excluded an additional 116 subjects with major protocol deviations identified during re-monitoring.

Reviewer comment: Although there were a large number of GCP violations noted for this study, the overwhelming majority were related to the informed consent process, which is unlikely to have a significant impact on immunogenicity or safety results of the study. Most of the other violations identified during re-monitoring were related to source documentation, and these violations would have only impacted safety data and would not likely affect the immunogenicity results of the study. This is confirmed by the re-analysis done by the applicant using the MPPS which showed that there was no significant change in the study endpoints with exclusion of additional subjects impacted by protocol deviations.

5.2.10 Efficacy Analyses

5.2.10.1 Analyses of Primary Endpoint(s)

Immunogenicity in 3 through 8 years age group

The results for the primary immunogenicity objective for subjects 3 through 8 years are shown in the table below. Results prior to re-monitoring, with all sites except the site in Mexico are shown in the Per Protocol Set (PPS) analysis. Results after re-monitoring and removal of additional subjects is shown in the Modified Per Protocol Set (MPPS) analysis.

Table 12. Results for Primary Objective in Subjects 3 through 8 Years (PPS and MPPS)

	PPS	**PPS**	**PPS**	**MPPS**	**MPPS**	**MPPS**
Seroconversion Rate	**Control N=455**	**Agriflu N=895**	**Difference in SCR (95% CI)**	**Control N=425**	**Agriflu N=844**	**Difference in SCR (95% CI)**
A/H1N1	94%	95%	-1% (-4, **-1**)	94%	95%	-1% (-4, **1**)
A/H3N2	87%	77%	10% (6, 14)	87%	78%	9% (5, 13)
B	85%	87%	-2% (-6, **2**)	85%	87%	-2% (-6, **2**)

Geometric Mean Titers (GMTs)	**Control N=456**	**Agriflu N=895**	**GMT Ratio (95% CI)**	**Control N=425**	**Agriflu N=845**	**GMT Ratio (95% CI)**
A/H1N1	57	42	1.32 (1.11, 1.56)	57	42	1.40 (1.16, 1.68)
A/H3N2	13	9.76	1.48 (1.34, 1.64)	13	9.73	1.39 (1.18, 1.63)
B	15	17	0.95 (0.84, **1.07**)	15	17	0.90 (0.77, **1.04**)

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_18, Table 11.4.1.1-3, 11.4.1.1-6; Addendum to V71_18 CSR Table 8.2-1, 8.2-2
Bolded text denotes parameters for which the noninferiority criteria were met

The criteria for demonstration of non-inferiority were met for 3 of the 6 endpoints. Both endpoints for A/H3N2 were missed, as well as the endpoint GMT ratio for A/H1N1. Comparing the outcomes using PPS versus MPPS datasets in Table 17, no significant impact on immunogenicity results was observed after re-monitoring and the same endpoints failed before and after re-monitoring.

Immunogenicity in 9 through 17 years age group

Immunogenicity in subjects 9 through 17 years was not evaluated in this study, as this age group was previously studied in V71P5, a phase III, observer-blind, randomized, controlled, multicenter study to evaluate safety, tolerability, and immunogenicity of two trivalent subunit inactivated influenza vaccines (Agrippal and Fluvirin) in healthy children aged 3 through 8 years, in healthy children/adolescents aged 9 through 17 years and in healthy adults aged 18 through 64 years. Agrippal is the trade name under which Agriflu is licensed in Europe. For details regarding this study, please see clinical review for initial approval for Agriflu under STN 125297/0. Briefly, V71P5 was non-comparative in design and immunogenicity results for the 9 through 17 years age cohort, studied as a secondary objective of the protocol, showed that both Agrippal and Fluvirin were able to meet CBER immunogenicity criteria for accelerated approval based on seroconversion rate and percent of subjects with post-vaccination HI titer $\geq$1:40.

Reviewer comment: The immunogenicity results for the 9 through 17 years age range from V71P5 would only be sufficient for accelerated approval as it is non-comparative in nature. Extrapolation of vaccine effectiveness in this age range would be reasonable if efficacy is shown in the younger pediatric population and adult population. Although clinical disease endpoint efficacy has been demonstrated in the adult population 18 years and older, study V71_18 was not able to demonstrate non-inferiority of Agriflu against a licensed comparator in the younger pediatric population of 3 through 8 years. Thus, there is inconclusive evidence for the effectiveness of Agriflu for the 9 through 17 years age range.

5.2.10.2 Analyses of Secondary Endpoints

Table 13. Results for Secondary Immunogenicity Objective in Subjects 3 through 8 Years (PPS)

Subjects with Post-Vaccination HI Titer $\geq$1:40	**Agriflu N=895**	**Control N=456**
A/H1N1	97% (**95**, 98)	95% (**93**, 97)
A/H3N2	100% (**100**, 100)	100% (**99**, 100)
B	95% (**93**, 96)	92% (**89**, 94)
Seroconversion Rate	**Agriflu N=894**	**Control N=456**
A/H1N1	95% (**93**, 96)	94% (**91**, 96)

A/H3N2	77% (**74**, 80)	87% (**84**, 90)
B	87% (**84**, 89)	85% (**81**, 88)

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_18, Table 11.4.1.2-3, 11.4.1.1-6
Bolded text denotes parameters for which criteria were met

CBER criteria for percentage of subjects achieving HI titer ≥1:40 and for seroconversion was met for all three strains contained in the vaccine for Agriflu as well as the control vaccines.

Reviewer comment: Reanalysis of the data after re-monitoring did not meaningfully change the secondary immunogenicity results.

5.2.11 Safety Analyses

5.2.11.1 Methods

Safety results were presented for three different groups based on age and control vaccine: 3 to <4 years of age [Agriflu (N=97) versus Fluzone (N=48)], 4 through 8 years of age [Agriflu (N=942) versus Fluvirin (N=483)], and 9 through 17 years of age [Agriflu (N=817) versus Fluvirin (N=412)]. Information on solicited adverse reactions was collected for the seven days post-vaccination, information on all unsolicited adverse events (AEs) was collected for the 21 days post-vaccination, and information on SAEs was collected for the entire study period.

Re-analysis of the safety data was done after re-monitoring to exclude subjects who had discrepancies in data among source documentation. This led to the exclusion of 24% of Agriflu, and 21% of control subjects from analysis after first vaccination; and exclusion of 26% of Agriflu, and 22% of control subjects after second vaccination. There was no new safety signal in the safety results after re-monitoring. The tables presented below are from the primary safety analysis prior to exclusion of additional subjects.

5.2.11.2 Overview of Adverse Events

Table 14. Percentage of Subjects with Adverse Reactions and Adverse Events by Age (SP)

	3 to <4	3 to <4	4 to 8	4 to 8	3 to 8y	3 to 8	9 to 17	9 to 17
	Agriflu	Fluzone	Agriflu	Fluvirin	Agriflu	Control	Agriflu	Fluvirin
Number of subjects	96	48	941	483	1037	531	817	412
Any solicited AR	56%	54%	46%	52%	47%	52%	43%	43%
Any solicited local AR	42%	48%	34%	40%	35%	41%	33%	36%
Any solicited systemic AR	31%	33%	25%	30%	25%	30%	24%	23%
Any unsolicited AE	46%	63%	37%	34%	38%	37%	12%	14%
Any SAE	3%	2%	1%	<1%	1%	1%	<1%	1%

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_18, Table 12.2.1.1-1, 12.2.1.2-1

Agriflu appears to have slightly lower rate of adverse reactions compared to the control in the 3 through 8 years age group. Percentages of ARs in the older age group of 9 through 17 years were similar between the two groups.

Table 15. Percentage of Subjects with Local Solicited AR by Age (SP)

	3 to <4	3 to <4	4 to 8	4 to 8	3 to 8y	3 to 8	9 to 17	9 to 17
	Agriflu	Fluzone	Agriflu	Fluvirin	Agriflu	Control	Agriflu	Fluvirin
Number of subjects	96	48	941	483	1037	531	817	412

Ecchymosis	0	0	<1%	0	<1%	0	<1%	0
Erythema	0	1%	<1%	0	<1%	<1%	<1%	<1%
Induration	0	2%	1%	1%	1%	1%	1%	1%
Swelling	0	2%	1%	2%	1%	2%	1%	2%
Pain	42%	48%	34%	40%	35%	40%	33%	35%
Severe pain	1%	0	1%	1%	1%	1%	1%	1%

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_18, Table 12.2.3.1-1

The percentages of subjects with ecchymosis, erythema, induration, and swelling were low in each arm (all ≤2%) and are consistent to what is reported in adults in the package insert for Agriflu. While pain was reported commonly, the percentages of subjects with pain were similar in each arm and severe pain was rare (all ≤1%).

Table 16. Percentage of Subjects with Generalized Solicited AR by Age (SP)

Age in years	3 to <4	3 to <4	4-8	4-8	3-8	3-8	9-17	9-17
	Agriflu	Fluzone	Agriflu	Fluvirin	Agriflu	Control	Agriflu	Fluvirin
Number of subjects	96	48	941	483	1037	531	817	412
Chills	3%	8%	4%	3%	4%	4%	5%	2%
Malaise	11%	21%	7%	8%	7%	10%	8%	7%
Myalgia	11%	23%	7%	8%	8%	9%	7%	8%
Arthralgia	4%	6%	4%	4%	4%	4%	3%	3%
Headache	13%	8%	9%	10%	10%	10%	11%	9%
Sweating	5%	4%	3%	6%	4%	5%	5%	5%
Fatigue	3%	4%	3%	4%	3%	4%	6%	5%
Fever	13%	2%	11%	14%	11%	13%	5%	3%
Fever >40 C	0	0	<1%	<1%	<1%	<1%	1%	<1%
Analgesic/Antipyretic use	13%	10%	8%	10%	9%	10%	3%	2%

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_18, Table 12.2.3.1-3

Myalgia, malaise, and headache were the most commonly reported solicited generalized adverse reactions in this study. Overall, the rate of generalized solicited AR is comparable between Agriflu and the comparator for the 3 through 8 years age group and 9 through 17 years age group. Of note, fever was reported in 13% of Agriflu subjects compared to 2% of placebo subjects in the 3 to <4 years age cohort. No increase in the rate of fever was noted in the 4 through 8 years old age group, and no increase in severe fever i.e., fever >40° Celsius was observed in the study.

Reviewer comment: In study V70_29 in pediatric subjects 6 to <72 months, the frequency of fever after vaccination was comparable between the Agriflu group and the non-adjuvanted comparator group. Per the product label for Fluzone, the fever rate in the 3 through 8 years age range was approximately 7%. The 2% fever rate for Fluzone observed in this study for the 3 to <4 years age range appears to be an under-representation of the true fever rate for Fluzone; and the finding could reflect the limited sample size of the current trial compared to the Fluzone effectiveness studies which support Fluzone labeling. Importantly, an imbalance in the frequency of fever events was not observed between the Agriflu and the Fluzone study arms in pediatric subjects 6 to <72 months in study V70_29.

The most commonly reported unsolicited AEs in the 3 through 8 years age group were upper respiratory infection, nasopharyngitis, and pyrexia. The most commonly reported unsolicited AEs in the 9 through 17 years age group were nasopharyngitis, upper

respiratory tract infection, and cough. The percentages of subjects with each of these AEs were similar in the Agriflu and control arms.

5.2.11.3 Deaths

There were no deaths reported during this study.

5.2.11.4 Nonfatal Serious Adverse Events

Serious adverse events occurring in the 30 days post-vaccination period were reported in 8 subjects who received Agriflu and in 2 control subjects. Only one SAE was assessed to be possibly related to study vaccine; this was a case of bronchopneumonia in a 3-year old female subject in the Agriflu arm. The subject complained of cough, headache, fever, and chills a few hours after receiving the second dose of the study vaccine. Her condition worsened over the next few days with increased respiratory difficulty. She was hospitalized 6 days after the second vaccination with the diagnosis of pneumonia, and treated with intravenous fluids, oxygen, and antibiotics. The subject had complete recovery.

Reviewer comment: The SAE case report for above subject was reviewed. Given the timing of onset of symptoms (around time of 2nd vaccine administration, 4 weeks after 1st vaccine dose) and subject's final diagnosis of bacterial pneumonia, it is unlikely that this event was related to the study vaccine.

5.2.11.5 Dropouts and/or Discontinuations

Three subjects who received Agriflu were discontinued prematurely from the study because of pallor; however, the reason for premature study discontinuation was classified as withdrawn consent.

5.2.12 Study Summary and Conclusions

V71_18 evaluated the immunogenicity of Agriflu in subjects 3 through 8 years, and the safety in the entire 3 through 17 years age range. Agriflu failed to meet 3 out of the 6 primary immunogenicity endpoints for demonstration of non-inferiority against a licensed influenza comparator vaccine. While re-analysis of data from before and after re-monitoring did not change the results for the immunogenicity endpoints, the findings from the study should be interpreted with caution given the multiple GCP violations and data integrity issues noted at multiple study sites.

No immunogenicity data were collected in subjects 9 through 17 years in this study. The applicant submitted results from study V71P5 to provide immunogenicity data in the older pediatric population. However, immunogenicity in this study was non-comparative and did not provide definitive evidence regarding vaccine effectiveness.

Safety of Agriflu was comparable to the licensed comparator vaccine and there are no safety signals to suggest that this vaccine is unsafe for this pediatric population. Overall, given the missed endpoints affected multiple vaccine strains, and the multitude of GCP issues which may have confounded study results, there is insufficient evidence to conclude that the vaccine is effective or ineffective in this pediatric population.

5.3 Study V71_22

Study V71_22 was a phase IV safety and immunogenicity study to evaluate Agriflu compared to a licensed comparator influenza vaccine in healthy subjects 50 years of age and older.

5.3.1 Objectives

The co-primary immunogenicity objectives were to demonstrate non-inferiority of:

- The post-vaccination (Day 22) hemagglutination inhibition (HI) geometric mean titers (GMTs) of Agriflu over the corresponding GMTs of the comparator vaccine for all three influenza strains, in healthy adults aged 50 years and above and,
- The percentages of subjects achieving seroconversion in antibody titers on Day 22 in the Agriflu group over the corresponding percentages in the control group for all three influenza strains, in healthy adults aged 50 years and above.

The secondary immunogenicity objective was to evaluate immunogenicity in terms of percentage of subjects with HI titer ≥ 10, seroconversion rates, and GMT ratios of Agriflu and of the control in healthy adults by age cohort (50-64 years and ≥ 65 years).

The safety objective was to evaluate the safety and tolerability of Agriflu and the control in healthy adults age 50 years and older.

5.3.2 Design Overview

Subjects were stratified by age cohort, ≥ 50 years through 64 years, and ≥ 65 years; and by study center. Subjects were then randomized in a 1:1 ratio to receive Agriflu or Fluvirin on Day 1. Subjects were followed solicited local and systemic AEs from Day 1 through Day 7, and followed for AEs, SAEs, NOCDs, and AEs leading to withdrawal through Day 22. Blood for immunogenicity assays was collected pre-vaccination on day 1 and on Day 22.

5.3.3 Population

The study enrolled males and females 50 years of age and older who were in good and stable health as determined by history and physical examination.

5.3.4 Study Treatments or Agents Mandated by the Protocol

<u>Agriflu</u>
A 0.5mL dose of Agriflu contains purified viral envelope-glycoproteins NA and HA, including 15ug of HA of each of the three influenza strains, A/H1N1, A/H3N2, and B.
Lot #: C51P04H1, E51P05N1

<u>Fluvirin</u>
A 0.5mL dose of Fluvirin contains purified viral envelope-glycoproteins NA and HA, including 15ug of HA of each of the three influenza strains, A/H1N1, A/H3N2, and B.
Lot #: 123402A, 13382P

5.3.5 Sites and Centers

The study was conducted at 24 sites in four countries: South Africa (15 sites), the Philippines (4 sites), Thailand (3 sites), and Czech Republic (2 sites).

5.3.6 Surveillance/Monitoring

Table 17: Times and events table

Study Day	Day 1	Day 3	Day 7	Day 22
Procedures performed	-ICF -Eligibility -Medical history -Physical examination -Pregnancy test -HIV screening test -Serology blood draw -Study vaccine -30 minutes postinjection assessment -Dairy card dispensed -Assess all AEs -Assess SAEs -Assess Aes leading to withdrawal -Concomitant medications	-Diary card completion reminder	-Diary card completion reminder	-Physical examination -Pregnancy test -Serology blood draw -Diary card reviewed and collected -Assess all Aes -Assess SAEs -Assess Aes leading ot withdrawal -Concomitant medications -Study termination

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_22, Tables 9.5.1-1

5.3.7 Endpoints and Criteria for Study Success

Noninferiority of Agriflu versus Fluvirin would be demonstrated if the upper limit of the 2-sided 95% confidence interval (CI) on the ratio of GMTs ($GMT_{Fluvirin}$ / $GMT_{Agriflu}$) did not exceed the noninferiority margin of 1.5 and the upper limit of the 2-sided 95% confidence interval (CI) on the difference between the seroconversion rates ($Seroconversion_{Fluvirin}$ – $Seroconversion_{Agriflu}$) not exceeded 10 percentage points.

Reviewer comment: These success criteria for demonstration of noninferiority are reasonable for influenza vaccines.

5.3.8 Statistical Considerations & Statistical Analysis Plan

See statistical review for detailed description of statistical analysis.

5.3.9 Study Population and Disposition

5.3.9.1 Populations Enrolled/Analyzed

Exposed Set: all subjects who received a study vaccination

Full Analysis Set (FAS): all subjects who received one study vaccination and provided immunogenicity data at baseline and visit 2

Per Protocol Set (PPS): all subjects in the FAS who received the vaccine to which they were randomized, had no major protocol violations, did not have laboratory-confirmed influenza within 21 days of vaccination, and were not excluded due to other reasons

Safety Population (SP): all subjects in the Exposed Set with safety data.

5.3.9.1.1 Demographics

Table 18: Demographic Characteristics of Subjects in the All Enrolled Set for Study V71_22

	Agriflu N=1452	Fluvirin N=1450	Total N=2902
Mean Age (Years)	64.2	64.2	64.2

% Male	35%	38%	37%
Asian	33%	33%	33%
Black	11%	11%	11%
Caucasian	37%	36%	36%
Other	20%	21%	20%
Previously vaccinated against Influenza	33%	33%	33%

Source: Adapted from sBLA 125297/118; Clinical Study Report V70_29 Table 11.2-1

Baseline and key demographic characteristics were balanced between the two arms. The majority of subjects were female (63% of the total study population).

Reviewer comment: The demographics of this study is reflective of the populations in which the study was conducted and is not representative of the U.S. population. It is also expected that compared to the study population, the U.S. population may have a higher percentage of individuals who have received influenza vaccination previously.

5.3.9.1.2 Subject Disposition

The percentage of subjects who prematurely discontinued the study was 1% or less in each arm and balanced between the arms.

5.3.10 Efficacy Analyses

5.3.10.1 Analyses of Primary Endpoint(s)

Table 19: Results for Primary Objective of Non Inferiority Analysis for V71_22 (PPS)

GMT	**Fluvirin** N=1397	**Agriflu** N=1401	**GMT ratio Fluvirin/Agriflu (95% CI)**
A/H1N1	581	315	1.85 (1.66, 2.06)
A/H3N2	1048	697	1.5 (1.38, 1.64)
B	36	36	1 (0.93, **1.08**)
SCR	**Fluvirin** N=1390	**Agriflu** N=1398	**Difference in SCR Fluvirin-Agriflu (95% CI)**
A/H1N1	84%	75%	9% (5.6, 11.5)
A/H3N2	85%	72%	13% (10.1, 16.1)
B	40%	41%	-1% (-5, **2.3**)

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_22 Table 11.4.1.1-1, 11.4.1.1-2
Bolded text denotes parameters for which non-inferiority criteria were met

As shown in the table above, the study did not meet 4 of the 6 pre-specified endpoints. Both A/H1N1 and A/H3N2 failed to demonstrate non-inferiority against Fluvirin based on both GMT ratio and seroconversion rates.

Reviewer comment: Individuals >50 years of age are currently included in the approved indication and usage section of the prescribing information for Agriflu. The initial licensure of Agriflu for the age range above >50 years was based on immunogenicity results showing that Agriflu was able to meet CBER immunogenicity criteria based on percentage of subjects with HI≥1:40 and percentage of subjects with seroconversion. The failed immunogenicity endpoints in this study raises questions regarding the effectiveness of this vaccine in the older population. However, without clinical endpoint

efficacy data, it is uncertain if the suboptimal immunogenicity findings would translate to a meaningful difference in clinical efficacy. It is reassuring that for individuals ≥65 years of age, who may be at higher risk of influenza related complications, Section 8.5 of the current Agriflu label states that the immune response in the geriatric population is lower compared to younger adults. Based on the totality of evidence, the language in Section 8.5 is adequate and no labeling changes are warranted.

5.3.10.2 Analyses of Secondary Endpoints

Non-inferiority analysis outcomes, categorized by age cohort, are shown in the table below. The same endpoints failed for each age subgroup as the overall age range.

Table 20: Non-inferiority Analysis by Age Cohort for V71_22 (PPS)

	50 to <65 Years	**50 to <65 Years**	**50 to <65 Years**	**≥65 Years**	**≥65 Years**	**≥65 Years**
GMT	**Fluvirin** N=691	**Agriflu** N=691	**GMT ratio Fluvirin/Agriflu (95% CI)**	**Fluvirin** N=706	**Agriflu** N=711	**GMT ratio Fluvirin/Agriflu (95% CI)**
A/H1N1	682	372	1.83 (1.58, 2.13)	467	251	1.86 (1.59, 2.17)
A/H3N2	966	691	1.4 (1.23, 1.58)	1175	724	1.62 (1.43, 1.84)
B	38	37	1.03 (0.92, **1.11**)	34	34	0.98 (0.89, **1.08**)
SCR	**Fluvirin** N=686	**Agriflu** N=688	**Difference in SCR Fluvirin-Agriflu (95% CI)**	**Fluvirin** N=704	**Agriflu** N=710	**Difference in SCR Fluvirin-Agriflu (95% CI)**
A/H1N1	87%	78%	9% (5.4, 13.5)	81%	73%	8% (3.2, 12)
A/H3N2	88%	78%	10% (5.9, 13.8)	82%	66%	16% (11.7, 20.6)
B	45%	44%	1% (-4.5, **6**)	35%	39%	-3% (-8.5, **1.6**)

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_22 Table 11.4.1.1-4,
Bolded text denotes parameters for which non-inferiority criteria were met

Immunogenicity results for the secondary objective of percentage of subjects with post-vaccination HI titer ≥1:40 and percentage of subjects who seroconverted is shown below.

Table 21: Results for Secondary Immunogenicity Objective for V71_22 (PPS)

	50 to <65 Years	**50 to <65 Years**	**≥65 years**	**≥65 years**
	Fluvirin N=691	**Agriflu N=691**	**Fluvirin N=706**	**Agriflu N=710**
Percentage of subjects with HI>1:40 post vaccination				
A/H1N1	96% (**94**, 97)	94% (**92**, 96)	92% (**90**, 94)	91% (**89**, 93)
A/H3N2	99% (**98**, 100)	99% (**99**, 100)	98% (**97**, 99)	99% (**98**, 99)
B	59% (55, 63)	58% (55, 62)	56% (52, 60)	59% (55, 62)
Seroconversion Rates				
A/H1N1	87% (**84**, 89)	78% (**74**, 81)	81% (**78**, 84)	73% (**70**, 77)
A/H3N2	88% (**85**, 90)	78% (**75**, 81)	82% (**79**, 85)	66% (**63**, 70)
B	45% (**41**, 49)	44% (**40**, 48)	35% (**32**, 39)	39% (**35**, 42)

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_22 Table 11.4.1.1-2, 11.4.1.1-3, 11.4.1.1-4, 11.4.1.1-6
Bolded text denotes parameters for which criteria were met

The secondary immunogenicity success criteria of lower limit of the 2-sided 95% CI for the percentage of subjects achieving an HI ≥1:40 should meet or exceed 70% (for subjects aged <65 years) or 60% (for subjects aged ≥65 years) was not met for either vaccine, for either age group, for the B strain. Both Agriflu and Fluvirin met the criteria for demonstration of seroconversion in both age groups for all 3 strains.

Reviewer comment: The B strain was the only strain to meet non-inferiority criteria in the primary immunogenicity analysis for Agriflu. However, as shown here, the B strain secondary endpoints for both Agriflu and Fluvirin failed to meet the pre-specified criteria based on percentage of subjects with post-vaccination HI titers ≥1:40. Taking together the immunogenicity outcomes for the primary and secondary endpoints, these findings raise concern regarding the effectiveness of Agriflu for all three influenza strains in the vaccine.

5.3.10.3 Dropouts and/or Discontinuations

About 96% of subjects in both arms were included in the Per Protocol Set for analyses of the primary endpoint.

5.3.11 Safety Analyses

5.3.11.1 Methods

Solicited local and systemic adverse reactions were collected via diary cards through 7 days post vaccination. Unsolicited adverse events, including serious adverse events and AEs leading to premature study discontinuation, were followed for the entire 21-day study period.

5.3.11.2 Overview of Adverse Events

The percentages of subjects with adverse reactions and adverse events are shown in the following table.

Table 22: Percentage of Subjects with Adverse Reactions and with Adverse Events (SP)

	Fluvirin	**Agriflu**
Number of subjects	**1433**	**1428**
Any solicited adverse reaction	39%	39%
Any solicited local adverse reaction	24%	24%
Any solicited general adverse reaction	27%	26%
Any unsolicited adverse event	11%	11%
Any SAE	<1%	<1%
Adverse events leading to premature study discontinuation	<1%	<1%
Death	0	<1%

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_22 Table 12.2.1-1, 12.2.1.2-1

Percentages of subjects with each individual local solicited adverse reaction are shown in the following table.

Table 23: Percentage of Subjects with Individual Local Solicited Adverse Reactions (SP)

	Fluvirin	**Agriflu**

Number of subjects	**1433**	**1428**
Pain	18%	19%
Severe pain	<1%	<1%
Erythema	7%	6%
Induration	5%	5%
Swelling	3%	4%
Ecchymosis	2%	2%

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_22 Table 12.2.3.1-1

The percentage of subjects with severe individual local solicited adverse reactions was < 1% for each individual adverse reaction; therefore, the results for severity of these reactions are not included. The percentages of subjects with any ecchymosis, erythema, induration, and swelling were low and were similar in the Fluvirin and Agriflu arms. While pain was reported more commonly, severe pain was rare.

The percentages of subjects with individual solicited generalized adverse reaction are shown in the following table.

Table 24: Percentage of Subjects with Individual Generalized Solicited Adverse Reactions (SP)

	Fluvirin	**Agriflu**
Number of subjects	**1433**	**1428**
Headache	11%	11%
Fatigue	10%	10%
Myalgia	10%	9%
Sweating	7%	7%
Malaise	7%	6%
Arthralgia	6%	6%
Chills	5%	5%
Loss of appetite	4%	3%
Nausea	3%	3%
Fever	1%	1%
Temperature >40 C	<1%	<1%

Source: Adapted from sBLA 125297/118; Clinical Study Report V71_22 Table 12.2.3.1-3

The most commonly observed solicited systemic adverse reactions were headache, fatigue, and myalgia. The percentage of subjects with each individual solicited systemic adverse reaction was similar in the two study arms. The percentage of severe individual systemic adverse reactions was ≤ 1% for each adverse reaction.

Unsolicited AEs

Each unsolicited AE was reported in ≤ 1% of subjects in either study arm and was balanced between the two arms. The most commonly reported unsolicited AEs were upper respiratory tract infection, nasopharyngitis, and headache.

5.3.11.3 Deaths

One death was reported. Subject (b) (6) a 65-year-old female with a history of hypertension, was vaccinated with Agriflu on (b) (6) and (b) (6) days later felt weak with left side chest body pain. The death certificate stated that the cause of death was natural causes; no autopsy was done. In the opinion of the investigator, her death was due to myocardial infarction that was not related to study vaccine.

Reviewer comment: Narrative of above event was reviewed, and the death does not appear to be related to the study vaccines.

5.3.11.4 Nonfatal Serious Adverse Events

SAEs were reported in 5 subjects in the Fluvirin arm and in 3 subjects in the Agriflu arm. None of the SAEs were judged by the investigator as vaccine related.

5.3.11.5 Dropouts and/or Discontinuations

Three subjects (2 in the Fluvirin arm and one in the Agriflu arm) discontinued prematurely from the study because of adverse events. All were due to SAEs: left basal ganglia hemorrhage (n=1; Fluvirin arm), cerebrovascular accident (n=1; Fluvirin arm), and death due to myocardial infarction (n=1; Agriflu arm).

5.3.12 Study Summary and Conclusions

The study failed to meet 4 of the 6 pre-specified immunogenicity endpoints and failed to demonstrate the non-inferiority of Agriflu to a US-licensed influenza comparator vaccine in subjects ≥50 years of age. However, these results are of uncertain clinical significance since there are no clinical disease endpoint efficacy data available for this age population. Safety was overall comparable between the two vaccines in this age group.

6. ADDITIONAL CLINICAL ISSUES

6.1 Special Populations

6.1.1 Human Reproduction and Pregnancy Data

No pregnancies were reported in the submitted studies as studies V70_29 and V71_18 were conducted in the pediatric populations and study V71_22 was conducted in an older adult population. There are insufficient data to establish the safety of Agriflu in pregnant women.

6.1.2 Use During Lactation

No data were reported regarding use during lactation in the submitted studies which were conducted in the pediatric and older adult populations.

6.1.3 Pediatric Use and PREA Considerations

Study V70_29 in subjects 6 to <36 months marginally missed 2 of the 6 prespecified endpoints for noninferiority, both for A/H1N1. Study V71_18 in subjects 3 through 8 years missed 3 of the 6 prespecified non-inferiority endpoints, affecting immunogenicity endpoints to 2 of the influenza strains contained in the vaccine. No comparative immunogenicity study is available for the 9 through 17 years age range. Safety in the entire age range of 6 months through 17 years was comparable to licensed Influenza comparator vaccines.

While there were multiple missed endpoints across the studies, the failed endpoints missed the pre-specified non-inferiority criteria by narrow margins. There is insufficient

evidence to conclude that the vaccine is unsafe or ineffective in pediatric populations. The results from the studies are also inadequate to conclude that the vaccine product is effective in the pediatric population given the failed endpoints affected multiple vaccine strains, across different seasons and in different study populations. Overall, the submitted studies provide inconclusive evidence for the effectiveness of Agriflu in children and adolescents 6 months through 17 years of age. This assessment was presented to the Pediatric Review Committee (PeRC) on October 8, 2019; and the PeRC agreed with CBER assessment.

Additionally, the two PREA-PMRs # 2 and 3 were fulfilled following the submission of the final study reports for V70_29 and V71_18

6.1.4 Immunocompromised Patients

Agriflu has not been studied in immunocompromised patients.

6.1.5 Geriatric Use

V71_22 was conducted in subjects ≥50 years of age and subgroup analysis was done for subjects 65 years of age and older. In this subgroup, the study failed to meet 4 of the 6 pre-specified immunogenicity endpoints to demonstrate non-inferiority against a licensed influenza comparator vaccine. The clinical significance of this is unclear as in earlier studies as well as this current study, Agriflu was able to meet CBER criteria for accelerated approval based on seroconversion rate and percentage of subjects with HI titer ≥1:40. No clinical endpoint efficacy data are available for individuals 50 year of age and older. The label does reflect that the antibody response in the elderly population is diminished compared to the younger adult population.

7. CONCLUSIONS

The submission fulfills the two pediatric post-marketing requirements as outlined in the Agriflu approval letter from November 2009. The data from the two pediatric studies V70_29 and V71_18 provide inconclusive evidence for the effectiveness of Agriflu in the pediatric population of 3 to <18 years.

This submission also contains a post-marketing commitment study, V71_22, to evaluate the immunogenicity of Agriflu compared to a licensed influenza vaccine in the population of adults 50 year of age and older. This study failed to meet the pre-specified immunogenicity success criteria to demonstrate non-inferiority, however without clinical endpoint efficacy data, it is uncertain if the suboptimal immunogenicity findings would translate to a meaningful difference in clinical effectiveness. By submitting the final study report for V71_22, the PMC #5 is considered as fulfilled.

8. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

8.1 Discussion of Regulatory Options

For the pediatric population 6 months through 17 years of age, given all the studies done are immunogenicity studies and the data are inconclusive to support the effectiveness of this vaccine in this age group, the applicant has the option of conducting a clinical disease endpoint efficacy study using Agriflu to demonstrate the effectiveness of this vaccine in the pediatric population, if they plan to pursue a pediatric indication. However, as this product is no longer marketed in the United States (b) (4)

(b) (4) the applicant will not be seeking an indication for use in children and adolescents and has no plans to conduct further studies in this age group.

For the population of individuals 50 years of age and older, although this product has an indication for use in this age group, the failed immunogenicity results from study V71_22 calls to question the effectiveness of this vaccine for this older age group. A discussion was held with the applicant via teleconference with a suggestion to limit the indication of Agriflu to individuals 18 to <50 years given the results of V71_22. The applicant responded that they are not willing to change the indication and usage as it would impact the existing contract with BARDA. Since there is no clinical disease endpoint efficacy data available in this age group which shows the product to be ineffective, and studies do not show the product to be unsafe, and in light of the convincing efficacy data in adults 18 through 49 years of age there is insufficient information to revoke the approved indication for individuals 50 years and older at this time. The label does contain language stating that the immune response in the geriatric population is diminished compared to younger adults, which is a correct representation of the available data from clinical studies in this age group.

8.2 Recommendations on Regulatory Actions

These three studies submitted fulfill the PMR/PMC requirements under the original Agriflu approval. There is no change in indication for the product based on these studies.

8.3 Labeling Review and Recommendations

Changes to the label include:

- Section 8.4: Indicated that studies done are inconclusive to establish effectiveness of this vaccine in the pediatric population.
- Section 8.1, 8.2: Updated PLLR language