BLA Clinical Review Memorandum

Application Type	1232
STN	125510/143
CBER Received Date	22 January 2019
PDUFA Goal Date	21 February 2020
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Rachel Zhang, MD
Review Completion Date / Stamped Date	20 February 2020
Supervisory Concurrence	Douglas Pratt, MD, MPH, Acting Branch Chief, Clinical Review Branch 1
Applicant	Seqirus, Inc
Established Name	Quadrivalent Influenza Vaccine, Adjuvanted
(Proposed) Trade Name	Fluad Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	15 µg of hemagglutinin per strain from each of the following four influenza subtypes or lineages: A/H1N1 A/H3N2 B/Yamagata B/Victoria Adjuvant (MF-59): Squalene (9.75mg) Polysorbate 80 (1.175 mg) Sorbitan trioleate (1.175mg) Sodium citrate dihydrate (0.66mg) Citrate acid monohydrate (0.04mg) Excipients: Neomycin ((b) (4)) Kanamycin ((b) (4)) Hydrocortisone ((b) (4)) Formaldehyde ((b) (4)) CTAB (≤12mcg) Ovalbumin (≤1.0mcg)
Dosage Form(s) and Route(s) of Administration	Suspension for injection supplied in 0.5 mL single-dose pre-filled syringes to be administered by intramuscular injection
Dosing Regimen	A single 0.5 mL dose to be given annually
Indication(s) and Intended Population(s)	Fluad Quadrivalent is an inactivated influenza vaccine proposed for active immunization against influenza subtypes A and type B contained in the vaccine. Fluad Quadrivalent is proposed for use in persons 65 years of age and older.
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	Adverse event
AESI	Adverse Event of Special Interest
aQIV	Adjuvanted Quadrivalent Influenza Vaccine
AR	Adverse Reaction
aTIV	Adjuvanted Trivalent Influenza Vaccine
BIMO	CBER Bioresearch Monitoring
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CSR	Clinical Study Report
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
HA	Hemagglutinin
HI	Hemagglutination Inhibition
ICH	International Conference on Harmonization
ILI	Influenza-Like Illness
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
NOCD	New Onset of Chronic Disease
OBE	Office of Biostatistics and Epidemiology
OVRR	Office of Vaccines Research and Review
PeRC	Pediatric Review Committee
PI	Package Insert
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PPS	Per Protocol Set
PREA	Pediatric Research Equity Act
PT	Preferred Term
QIV	Quadrivalent Influenza Vaccine
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
sBLA	Supplemental Biologics License Application
SCR	Seroconversion Rate
SOC	System Organ Class
STN	Submission Tracking Number
US	United States
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Fluad® (aTIV) is an adjuvanted, trivalent, inactivated, seasonal influenza virus vaccine containing 15 µg hemagglutinin (HA) antigen per virus strain (total dose of 45 µg) and a proprietary adjuvant, MF59C.1, and is currently licensed under accelerated approval for the prevention of influenza disease caused by influenza A subtype viruses and type B virus contained in the vaccine in persons 65 years of age and older. With this supplement, Seqirus is seeking approval for Fluad Quadrivalent (aQIV), an adjuvanted, quadrivalent, inactivated, seasonal influenza vaccine containing a second type B strain of a second lineage added to the aTIV formulation, for a total dose of 60 µg, indicated for active immunization against influenza disease caused by influenza A subtypes and type B viruses contained in the vaccine in the same age population. Fluad Quadrivalent therefore contains antigens from two influenza A subtype viruses (representing the H1N1 and H3N2 subtypes) and two type B viruses (representing the B/Victoria and B/Yamagata lineages). The Applicant is pursuing licensure of aQIV as a supplement to the existing aTIV vaccine license based on clinical immunogenicity data which met CBER criteria for accelerated approval, as described in the Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (May 2007).

Summary of Clinical Findings

Study V118_18 was a phase 3, randomized, observer-blind, controlled, multi-center study in adults 65 years of age and older to evaluate the efficacy, immunogenicity, and safety of Fluad Quadrivalent compared to a non-influenza vaccine comparator (Boostrix®). A total of 6790 subjects were enrolled and randomized 1:1 to receive one dose of aQIV or Boostrix on Day 1. Subjects were followed for influenza-like illness (ILI) symptoms and tested for influenza to measure vaccine efficacy. Serum samples for immunogenicity were assessed in a subset of enrolled subjects. Immunogenicity results demonstrated that aQIV was able to meet CBER criteria for accelerated approval based on percentage of subjects with HI titer $\geq$1:40 and percentage of subjects with seroconversion. The study failed to meet the pre-specified success criteria to demonstrate efficacy of aQIV against any reverse transcriptase polymerase chain reaction (RT-PCR) confirmed influenza. The majority of influenza cases in the study were A/H3N2 that was not antigenically matched to the strain contained in the vaccine. Safety data from the study showed that the rate of solicited adverse reactions was slightly higher in the aQIV group compared to the Boostrix group; however, there was no notable difference in the rate of severe adverse reactions. There were no notable differences in the rates of unsolicited adverse events or serious adverse events between the two groups.

Additional supportive safety data was provided by Study V118_20, a phase 3, randomized, double-blind, controlled, multicenter, clinical study designed to evaluate the safety and immunogenicity of aQIV in comparison with Fluad (aTIV-1) and an MF59-adjuvanted trivalent subunit influenza vaccine containing the alternate B strain (aTIV-2), in adults ages 65 years and older. A total of 1778 subjects were enrolled and randomized 2:1:1 to receive aQIV, aTIV-1, or aTIV-2. Subjects were followed for safety for 6 months. There was a slightly higher rate of solicited local adverse reactions in the aQIV group compared to the aTIV-1 and aTIV-2 groups. The rate of solicited systemic adverse reactions was similar among the groups. There were no notable imbalances in the rate of unsolicited adverse events or serious adverse events among the 3 groups.

In conclusion, the data submitted by the Applicant to sBLA 125510/143 support the approval of Fluad Quadrivalent for active immunization against influenza disease in adults 65 years of age and older under accelerated approval regulations (21CFR 601.41) based on HI antibody response as the surrogate endpoint for efficacy. Although clinical disease efficacy was not demonstrated based on the submitted study (V118_18), the Applicant will be required to conduct a confirmatory efficacy study post-licensure in order to obtain full traditional approval for aQIV. The risks of vaccination with aQIV are overall comparable to those of Fluad (aTIV) and other approved inactivated influenza vaccines. Thus, the overall risk-benefit profile of aQIV has been determined to be favorable.

Compliance with Pediatric Research Equity Act (PREA)
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups must be submitted at the time an application for approval of a formulation with a new active ingredient, unless the requirement for assessment has been deferred or waived.

For aQIV, a partial waiver for conducting studies in children from birth to <6 months of age was granted because the necessary studies are impossible or highly impracticable to conduct in this age group [Section 505B(a)(4)(i)]. A deferral was granted for children 6 months to <72 months of age [Section 505B(a)(3)]. A partial waiver was granted for children 6 years to <17 years of age because the product does not represent a meaningful therapeutic benefit over existing therapies for children in that age group and is not likely to be used by a substantial number of children in that age group [Section 505B(a)(5)(B)(iii))].

Recommendation for Regulatory Action
The clinical data submitted by the Applicant support the accelerated approval of Fluad Quadrivalent for active immunization of adults 65 years of age and older against influenza disease caused by the influenza subtypes A and type B viruses contained in the vaccine.

Recommendation on Postmarketing Action
As per accelerated approval regulations, the Applicant is required to study the vaccine further, to verify and describe its clinical benefit in a confirmatory clinical efficacy study of aQIV. No safety issues were identified in the pre-licensure data to warrant postmarketing requirements for additional safety evaluations. The proposed routine pharmacovigilance appears adequate.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The subgroup analyses of immunogenicity and safety by age, sex, and ethnicity generally were shown to be consistent with the overall immunogenicity and safety results.

1.2 Patient Experience Data

Patient experience data was not submitted as part of this application.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Influenza, a respiratory and systemic illness caused by influenza virus infection, is an important cause of infectious morbidity and mortality worldwide. Annual influenza epidemics are responsible for an estimated 3 to 5 million cases of severe respiratory illness and about 290,000 to 650,000 deaths worldwide each year (1). In the United States, an estimated 55,000 to 431,000 hospitalizations and 3,000 to 49,000 deaths are attributed to influenza each year (2, 3). Influenza causes morbidity in all ages, with the highest rates of serious morbidity and death among older adults and persons with specific underlying medical conditions, such as chronic pulmonary or cardiac disease (4, 5). In recent years in the United States, the cumulative hospitalization rate (per 100,000) for adults over 65 years of age was up to four times higher than that of adults 18-49 years of age (4,5). Adults ≥ 65 years of age also account for the majority (90%) of deaths from seasonal influenza in the United States (4,5).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, six FDA-licensed antiviral drugs are available for use in the United States [Tamiflu® (oseltamivir phosphate), Relenza® (zanamivir), Rapivab® (peramivir), Flumadine® (rimantidine), amantadine, and Xofluza® (baloxavir marboxil)]. Of these, only 4 are currently recommended for use by the Centers for Disease Control and Prevention: the neuraminidase inhibitors Tamiflu, Relenza, Rapivab; and the cap-dependent endonuclease inhibitor Xofluza, which was approved for use in October 2018. Although Xofluza is approved for use in persons 12 years of age and older, adults 65 years of age and older were not included in the initial published clinical trials (6). Use of adamantine class derivatives (amantadine and Flumadine) is no longer recommended because many strains of influenza, including the 2009 H1N1 influenza, are currently resistant to this class of drugs. Although neuraminidase inhibitors are currently effective against most seasonal influenza viruses, resistance to drugs in this class has developed sporadically (7). None of these drugs are indicated for the prevention of influenza.

2.3 Safety and Efficacy of Pharmacologically Related Products

Inactivated whole-virus influenza vaccines had been commercially available since the 1940s. Currently, seven inactivated trivalent standard dose (15 µg hemagglutinin (HA)/strain) influenza vaccines are licensed in the U.S for use in adults 65 years of age and older. These include Fluzone®, Flucelvax®, Fluvirin®, FluLaval®, Fluarix®, Agriflu®, and Afluria®. Fluad® is the only adjuvanted, inactivated trivalent standard dose influenza vaccine licensed in the U.S for use in adults 65 years of age and older. In addition, five standard dose, inactivated quadrivalent influenza vaccines are available for use in adults 65 years of age and older: Afluria Quadrivalent®, Fluarix Quadrivalent®, FluLaval Quadrivalent®, Fluzone Quadrivalent®, and Flucelvax Quadrivalent®. Flublok® and Flublok Quadrivalent® are recombinant protein influenza vaccines that contains 45 µg HA/strain and is licensed in the US for use in adults 18 years of age and older. Fluzone High-Dose (trivalent; 60ug HA/strain) and Fluzone High-Dose Quadrivalent are currently the only licensed high-dose inactivated influenza vaccines available for use in adults 65 years of age and older.

While standard dose trivalent and quadrivalent vaccines have been shown to be effective at preventing influenza infection in adults, few randomized, controlled studies have provided clinical efficacy data specifically for adults 65 years and older. Immune responses to yearly influenza vaccination are substantially lower in this older population, possibly due to decreased T-cell-dependent antibody responses, comorbidities, and functional disabilities observed in this population (8). Further, this population experiences disproportionate morbidity and mortality due to severe influenza infection.

In general, vaccination with inactivated influenza products is associated with mild to moderate injection site and systemic reactions. Adverse reactions seen in >10% of adults in one or more of the currently approved inactivated influenza vaccine products include, pain, redness, swelling, headache, fatigue, malaise, myalgia, and arthralgia. The most common (≥10%) adverse reactions observed with Fluad (aTIV) administration consist of injection site pain (25%) and tenderness (21%), myalgia (15%), headaches (13%), and fatigue (13%) (9). Evidence for a causal relation of Guillain-Barré Syndrome (GBS) with inactivated influenza vaccines is inconclusive. If an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated (10).

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

Fluad was licensed in the United States (US) on November 24, 2015 under accelerated approval regulations for use in persons 65 years of age and older. Fluad is currently approved for marketing in 27 countries worldwide. Cumulative worldwide exposure to Fluad is estimated to be 127 million individuals. There has been no increase in reporting frequency or event severity of any identified or potential risks associated with Fluad. Therefore, the benefit-risk balance remains unchanged based on the collective post-marketing experience to date. Effectiveness of Fluad against clinical endpoint disease has not been established in a prospective, randomized, controlled trial.

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

Study V118_20 was submitted initially as the sole study to support the accelerated approval of Fluad Quadrivalent under this sBLA. Upon preliminary review, although the study was able to meet one of its two co-primary endpoints of demonstration of non-inferior immunogenicity of aQIV against aTIV and aTIV containing an alternate B strain, it was noted that the second primary endpoint of immunogenicity criteria needed to support accelerated approval (percentage of subjects with HI titer ≥1:40 and percentage of subjects with seroconversion) was met for both A strains but not met for either B strain in aQIV, as well as for the B strain contained in both aTIV vaccines included in the study. These immunogenicity results differed significantly from those observed with aQIV in Study V118_18 (previously included in a meeting package submitted to a related IND) and those seen in the Fluad (aTIV) study V70_27. An Information Request (IR) was sent to the Applicant on March 8, 2019 to request an explanation on the immunogenicity results observed for the B strains in Study V118_20. In a response submitted on March 14, 2019, the Applicant hypothesized that the lower immunogenicity observed for the B strains in Study V118_20 was likely due to inter-laboratory variability as a result of (b) (4) used for testing. This investigative conclusion was assessed as plausible by CBER's manufacturing, and controls (CMC) review team for this file. With input from the CMC team, the Applicant conducted a post-hoc study which re-tested a subset of samples from V118_20 using the V118_18 assay protocol. In the study report submitted June 25, 2019, the Applicant was able to demonstrate a substantial increase

in GMT titers and the proportion of subjects with HI titers ≥1:40 for both B strains in the randomly selected subset of subjects from study V118_20, with the testing protocol and reagents utilized for V118_18. Given the overall uncertainty regarding the interpretability of the immunogenicity analyses in Study V118_20, the review team concluded that the immunogenicity data from this study would not be adequate to support the accelerated approval of aQIV, although the safety results from this study could still be reviewed given the assay variability did not impact the safety data. The above-stated deficiency from V118_20 was brought to the Applicant's attention. The Applicant submitted additional data from a separate phase 3 study (V118_18) to the sBLA with the intention of addressing the CBER review issues. Based on all available data submitted to this sBLA, the review team concluded that immunogenicity and safety data from Study V118_18 would serve as the primary evidence to support accelerated approval of aQIV. Study V118_20 would be used to provide additional supportive safety data. Due to the substantial amount of new data submitted with V118_18 to this sBLA, it was considered to be a major amendment and the review clock was extended an additional three months.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized to accommodate the conduct of a complete clinical review without undue difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

According to the Applicant, the studies submitted with this supplement were conducted in accordance with the standards established by the Declaration of Helsinki and compliant with the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP) as well as with all local and/or national regulations and directives.

CBER Bioresearch Monitoring (BIMO) inspections were conducted at four study sites (Site #266 and #267 used for Study V118_18, and Site #103 and #117 used for Study V118_20). No substantial issues were identified at any of the sites. Please see the review memo by the Office of Compliance and Biologics Quality for additional details.

3.3 Financial Disclosures

In accordance with 21 CFR 54, the Applicant submitted FDA Form 3454 with this supplement, certifying that the Applicant had not entered into any financial arrangement with any clinical investigators involved in the trials comprising this licensure application, whereby the value of compensation to the investigator could be affected by the outcome of the study, as defined in 21 CFR 54.2(a). The Applicant also certified that each listed clinical investigator required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) did not disclose any such interests. The Applicant certified that no investigators were the recipients of significant payments as defined in 21 CFR 54.2(f).

Covered clinical studies (name and/or number): V118_18, V118_20		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 303		
Number of investigators who are employees of Seqirus, Inc. (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Review of the chemistry, manufacturing, and controls (CMC) data submitted in this supplement was conducted by Dr. Hang Xie from OVRR/Division of Viral Products. Please see the CMC review memo for additional details.

4.2 Assay Validation

Review of the assay validation data submitted in this supplement was conducted by Dr. Hang Xie from OVRR/Division of Viral Products. Please see the CMC review memo for additional details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vaccination against influenza results in an antibody response that can be quantified by elevation in serum HI titers. Some studies and meta-analyses associate HI titers ≥ 1:40 with 50% reduction in the risk of contracting influenza, based on controlled, influenza challenge studies in adults (11). Because these studies were conducted in young adults and used attenuated challenge viruses to assess protection, induction of HI titer $\geq$ 1:40, has not been proven to correlate with protection of older adults from illness due to wild-type influenza viruses (12). Indeed, vaccine failures have been described in association with high HI titers previously thought to be protective (13), indicating that continued work needs to done to establish correlates of protection to support licensure of novel influenza vaccines in all populations, but particularly in older adults and others at high risk for influenza infection.

The MF59C.1 adjuvant is an oil-in-water emulsion with a squalene internal oil phase and a citrate buffer external aqueous phase, stabilized by two nonionic surfactants, sorbitan trioleate and polysorbate 80 (synonymous with MF59 in this review memo; C.1 signifies citrate buffer), which is manufactured to generate uniform (165 nm in diameter) squalene oil droplets (14). The squalene oil is a biosynthetic precursor of cholesterol and steroid hormones; and is fully biodegradable. In humans, MF59 has been used in the experimental setting to increase antibody affinity and breadth of epitope recognition to

vaccination with pandemic influenza strains H5N1 and H1N1; however, these immunologic effects has yet to be linked directly to clinical effectiveness (15, 16).

4.5 Statistical

Statistical review of the clinical data submitted in this supplement was conducted by Dr. Ying (Charles) Cheung from OBE/Division of Biostatistics. Please see the statistical review for additional details.

4.6 Pharmacovigilance

Review of the pharmacovigilance plan for Fluad Quadrivalent was conducted by Dr. Graca Dores from OBE/Division of Epidemiology. Please see the pharmacovigilance review memo for additional details.

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

5.1 Review Strategy

Study V118_18 serves as the main evidence for accelerated approval of Fluad Quadrivalent. Study V118_20, also submitted to this BLA, provides additional supportive safety data for the study population. Other findings from studies V118_18 and V118_20 which were not critical to the regulatory decision-making and which did not contribute to product labeling are presented briefly.

The following sections were deleted from this review as they were not applicable to this application: 4.4.2: Human Pharmacodynamics, 4.4.3: Human Pharmacokinetics, 5.4: Consultations, 6.1.5: Directions for Use, 6.1.10.1.2: Medical/Behavioral Characterization of the Enrolled Population, 6.1.11.5: Exploratory and Post Hoc Analyses, 6.1.12.6: Clinical Test Results, 7: Integrated Overview of Efficacy and 8: Integrated Overview of Safety, 9.2 Aspects of Clinical Evaluation not Previously Covered.

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

The following files served as the basis for the clinical review:

STN 15510/143.0 modules:

- 1.3.4 Financial Certification and Disclosure
- 1.9 Pediatric Administrative Information
- 1.14 Labeling
- 2.5 Clinical Overview
- 2.7 Clinical Summary
- 5 Clinical Study Reports

STN 15510/143.3 module 5 Clinical Study Reports
STN 15510/143.4 module 5 Clinical Study Reports
STN 15510/143.5 modules:

- 1.3.4 Financial Certification and Disclosure
- 5 Clinical Study Reports

STN 125510/143.6 module 5.3.5.3 V118_18_20 Cross Study Serology Retest Report
STN 15510/143.7 modules:

- 2.5 Clinical Overview
- 2.7 Clinical Summary

STN 15510/143.8 module 1.9.6 Amendment PSP Final Draft

STN 15510/143.13 module 1.9 Pediatric Administrative Information
Amendments 11, 15, 16, 19, and 20 were reviewed for materials relevant to labeling.

5.3 Table of Studies/Clinical Trials

Table 1: Clinical Studies Included in sBLA 125510/143

Study Number; Population; Start/End Dates	Study Description	Study Objectives	Test Products, Number of Subjects Exposed	Number of Centers, Countries
V118_18 Adults ≥ 65 years of age 30 Sept 2016 to 23 July 2018	Phase 3, randomized, observer-blind, controlled, multi-center study	Efficacy, safety, and immunogenicity of aQIV vs non-influenza vaccine comparator	aQIV: 3381 Boostrix: 3380	89 centers Bulgaria, Colombia, Czech Republic, Estonia, Latvia, Lithuania, Malaysia, Philippines, Poland, Romania, Thailand, Turkey
V118_20 Adults ≥ 65 years of age 17 Oct 2017 to 17 May 2018	Phase 3, randomized, double-blind, controlled, multi-center study	Safety and immunogenicity of aQIV vs aTIV-1 (Fluad) and aTIV-2 (containing the alternate B strain)	aQIV: 888 aTIV-1 (Fluad): 444 aTIV-2: 444	20 centers United States

Adapted from BLA 125510/143, CSR 118_18, CSR 118_20

5.5 Literature Reviewed

1. World Health Organization. Influenza (Seasonal). WHO Fact Sheet. accessed Jan 2020 at: https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal)
2. Thompson, MG, et al. Influenza Div, National Center for Immunization and Respiratory Diseases, CDC. Estimate of Deaths Associated with Seasonal Influenza-United States, 1976-2007. MMWR August 27, 2010; 59(33);1057-1062. Retrieved from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5933a1.htm
3. Centers for Disease Control and Prevention (CDC). Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. Morb Mortal Wkly Rep. 2010 Aug 27;59(33):1057-62.
4. Epperson S, Blanton L, Kniss K, Mustaquim D, Steffens C, Wallis T, Dhara R, Leon M, Perez A, Chaves S, Abd Elall A, Gubareva L, Xu Xiyan, Villaneuva J, Bresse J, Cox N, Finelli L, Brammer L. Influenza Activity – United States, 2013-14 Season and Composition of the 2014-15 Influenza Vaccines. MMWR June 6, 2014, 63(22); 483-490. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6322a2.htm
5. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, Fukuda K. Influenza-associated hospitalizations in the United States. JAMA. 2004 Sep 15;292(11):1333-40.
6. Hayden FG, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl Med 6 Sept 2018; 379:913-923.
7. Uyeki TM, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional

Outbreak Management of Seasonal Influenza. CID, vol 68, Issue 6, 15 March 2019:e1-e47.
8. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. Ann Intern Med. 1995;123:518-27.
9. Fluad® [Package Insert]. Seqirus, Inc., Summit, NJ; April 2019. Accessed November 13, 2019.
10. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré Syndrome and the 199201993 and 1993-1994 influenza vaccines. N Engl J Medicine 1998; 339:1797-180.
11. Hobson D, Curry RL, Beare AS, Ward- Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J. Hyg. (Lond.) 70(4),767–777 (1972).
12. Reber A, Immunological assessment of influenza vaccines and immune correlates of protection. Expert Rev Vaccines 12 (5):519-536 (2013).
13. Ohmit SE, Petrie JG, Cross RT, Johnson E, Monto AS. Influenza hemagglutination inhibition antibody titer as a correlate of vaccine-induced protection. J. Infect. Dis. 204(12), 1879–1885 (2011).
14. O'Hagan DT. MF59 is a safe and potent vaccine adjuvant that enhances protection against influenza virus infection. Expert Rev Vaccines. Oct 5, 2007; 699–710.
15. Khurana S, Verma N, Yewdell JW, Hilbert AK, Castellino F, Lattanzi M, Del Giudice G, Rappuoli R, Golding H. MF59 adjuvant enhances diversity and affinity of antibody-mediated immune response to pandemic influenza vaccines. Sci Transl Med. Jun 1, 2011; 3(85):85ra48. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21632986.
16. Khurana S, Chearwae W, Castellino F, Manischewitz J, King LR, Honorkiewicz A, Rock MT, Edwards KM, Del Giudice G, Rappuoli R, Golding H. Vaccines with MF59 adjuvant expand the antibody repertoire to target protective sites of pandemic avian H5N1 influenza virus. Sci Transl Med. Jan 20, 2010; 2(15):15ra5.
17. Hak EF. Development and validation of a clinical prediction rule for hospitalization due to pneumonia or influenza or death during influenza epidemics among community dwelling elderly persons. J Infect Dis 2004; 189(3):450-458.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 V118_18

Study V118_18 was a Phase III, randomized, observer-blind, controlled, multicenter clinical study to evaluate the efficacy, safety and immunogenicity of Fluad Quadrivalent compared to a non-influenza comparator vaccine (Boostrix®) in adults ≥65 years of age.

6.1.1 Objectives

Key study objectives are listed below.

Primary Objective:
To demonstrate absolute vaccine efficacy (VE) of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence RT-PCR confirmed influenza, due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine, in subjects ≥65 years of age.

Secondary Immunogenicity Objective:

To evaluate the immunogenicity of aQIV measured by Hemagglutination inhibition (HI) titer 21 days after vaccination, against influenza strains homologous to the seasonal vaccine.

Safety Objectives:

- To evaluate the safety of aQIV through assessment for local and systemic solicited adverse reactions through Day 7 in a subset of subjects.
- To evaluate the rates in each vaccine group of unsolicited adverse events (AEs) for 21 days after vaccination and AEs leading to withdrawal, serious adverse events (SAEs), adverse events of special interest (AESI), and new onset of chronic disease (NOCD) for 365 days after vaccination.

Reviewer comment: The Applicant has also defined multiple other secondary and exploratory efficacy and immunogenicity objectives in the study protocol. These objectives will not be discussed in this review as they do not impact the clinical assessment of the product and the data do not contribute to labeling.

6.1.2 Design Overview

V118_18 was a Phase III, age stratified, randomized, observer-blind, non-influenza comparator-controlled, multicenter study conducted over the 2016-2017 Northern Hemisphere and 2017 Southern Hemisphere seasons. The study enrolled 6790 adults ≥ 65 years old who were healthy or had co-morbidities. Subjects were randomized in 1:1 ratio to receive one dose of Fluad Quadrivalent or Boostrix on Day 1. Serum samples were collected on Day 1 and Day 22 from a subset of 2801 enrolled subjects, in a 1:1 ratio to maintain study blind. After all the blood specimens had been obtained, the collected samples were then randomly selected in a 4:1 ratio (1362 aQIV; 340 Boostrix) for completing the analysis of the immunogenicity objectives. Additionally, all subjects received weekly phone calls or messages to assess for primary protocol-defined ILI symptoms [presence of at least one respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) concurrently with at least one systemic symptom (temperature of > 37.2°C/99°F, chills, tiredness, headache, or myalgia)] during the active ILI surveillance period, defined as from Day 1 through Day 181 or until the end of the influenza season, whichever was longer. Nasopharygneal (NP) swab collection for testing for influenza was done within 6 days after the first day of onset of primary protocol-defined ILI symptoms. Solicited reactions were collected for 7 days after vaccination in a subset of randomly selected subjects (1053 per vaccine group). Unsolicited adverse events (AEs) were collected up to Day 22 and serious adverse events (SAEs) and adverse events of special interest (AESIs) were collected through Day 366 in all subjects.

Reviewer comment: The ILI symptoms defined by the protocol for the primary endpoint appear to be broad and likely to be less specific for true influenza infections compared to a more specific definition such as the modified CDC definition of ILI (temperature >37.2°C and cough or sore throat).

6.1.3 Population

Inclusion Criteria:

1. Males and females ≥ 65 years old who were healthy or have had co-morbidities.
2. Individuals who or whose legal guardian had voluntarily given written consent after the nature of the study had been explained according to local regulatory

requirements, prior to study entry.
3. Individuals who had the ability to attend all scheduled visits and comply with study procedures.

Exclusion Criteria:

1. Receipt of diphtheria or Tetanus Toxoid or pertussis (acellular or whole cell) vaccines within the previous 5 years.
2. History of behavioral or cognitive impairment or psychiatric condition that, in the opinion of the investigator, may have interfered with the subject's ability to participate in the study.
3. History of any medical condition considered an AESI, see Section 7.1.4.1 of the protocol (Appendix 16.1.1).
4. Progressive or severe neurological disorder, seizure disorder, or history of Guillain-Barré syndrome.
5. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use was foreseen in this study.
6. Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous pertussis antigen-containing vaccine.
7. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws, including bleeding diathesis, or any other condition that may be associated with prolonged bleeding.
8. Abnormal function of the immune system resulting from:
    a. Clinical conditions.
    b. Systemic administration of corticosteroids. (oral/intravenous/intramuscular) at a dose equivalent to 20 mg of informed consent.
    c. Administration of antineoplastic and immunomodulating agents (e.g. Tumor Necrosis Factor [TNF] α antagonists or anti-B-cell antibodies) or radiotherapy within 1 year prior to informed consent.
9. Receipt of immunoglobulins or any blood products within 180 days prior to informed consent.
10. Receipt of an investigational or non-registered medicinal product within 30 days prior to informed consent or before completion of the safety follow-up period in another study and who were unwilling to refuse participation in another clinical study at any time during the conduct of this study (note: concomitant participation in an observational study not involving drugs, vaccines, or medical devices, was acceptable).
11. Study personnel or immediate family members (brother, sister, child, parent), the spouse of study personnel or individuals who were financially or emotionally dependent on study staff.
12. Receipt of any influenza vaccine within 6 months prior to enrolment in this study or who plan to receive influenza vaccine while participating in the study.
13. Receipt of any inactivated vaccine 14 days or live-attenuated vaccine 28 days prior to enrolment in this study or individuals who were planning to receive any vaccine within 28 days from study treatment.
14. Fever at the time of screening, defined as oral temperature ≥ 38.0°C (≥ 100.4°F). Enrollment could be considered if fever was absent for 72 hours.
15. Signs or symptoms of acute respiratory tract infection at the time of screening. Enrollment could be deferred if signs and symptoms were absent for 72 hours.
16. Residence in a chronic care facility (e.g. nursing home).

17. Participation in this trial in a prior season, if applicable.
18. Fatal prognosis of an underlying medical condition (< 12 months life expectancy).
19. Any other clinical condition that, in the opinion of the investigator, may have interfered with the results of the study or may have posed additional risk to the subject due to participation in the study.

Reviewer comment: Eligibility criteria were appropriate for this study and allow for generalizability to a population of adults 65 years of age and older.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Composition of aQIV and the comparator vaccine are shown in the tables below.

Table 2: aQIV Composition

Ingredients	Quantity Per Dose	Function
Active Ingredients Hemagglutinin (HA) and Neuraminidase (NA) antigens from the influenza virus strains NH 2016/17 season: A/California/7/2009pdm (NYMC X-181) (H1N1), A/HongKong/4801/2014 NYMC (X-263B) (H3N2), B/Brisbane/9/2014 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage). SH 2017 season: identical to NH 2016/17 season except that the H1N1 strain was replaced by A/Singapore/GP1908/2015 IVR-180	At least 15µg HA/strain	Active ingredient
Adjuvant		
Squalene	9.75 mg	Oil phase
Polysorbate 80	1.175 mg	Surfactant
Sorbitan trioleate	1.175 mg	Surfactant
Sodium citrate	0.66 mg	Buffer
Citric acid	0.04 mg	Buffer
Other Ingredients		
(b) (4)		
Water for injection	Up to 0.50 mL	Diluent

Adapted from BLA 125510/143, CSR 118_18, Table 2

Table 3: Boostrix Composition

Ingredient	Quantity Per Dose
Active Ingredients Diphtheria toxoid Tetanus toxoid Bordetella pertussis antigens Pertussis toxoid Filamentous Hemagglutinin Pertactin **Adjuvants** Adsorbed on aluminium hydroxide	 (b) (4) 2.5 Lf) (b) (4) (5.0 Lf) 8 µg 8 µg 2.5 µg ≤ 0.39 mg Al^{3+}
Other Ingredients Sodium chloride Water for injection	(b) (4) mg
Residues of special relevance	Polysorbate 80 (Tween 80) and formaldehyde

Adapted from BLA 125510/143, CSR 118_18, Table 4

Each 0.5 mL dose of vaccine was provided in a pre-filled syringe and administered intramuscularly in the region of the deltoid muscle.

6.1.6 Sites and Centers

The study was conducted in a total of 89 sites in 12 countries: Bulgaria (11), Colombia (7), Czech Republic (5), Estonia (6), Latvia (4), Lithuania (7), Malaysia (8), Philippines (6), Poland (15), Romania (8), Thailand (4), and Turkey (8).

6.1.7 Surveillance/Monitoring

Table 4: Surveillance Schedule

Study Day	1	3	15, 91, 271	22	181, 366
Procedure performed*	-vaccine -consent -medical history -physical exam -eligibility -randomization -30 minute post injection assessment -diary dispensed -assess all AEs, SAEs, NOCDs, AEs leading to withdrawal, ILI and AESIs -assess concomitant medications/ vaccinations -ILI instruction sheet dispensed -serology	-diary reminder call	-assess all AEs, SAEs, NOCDs, AEs leading to withdrawal, ILI and AESIs -assess concomitant medications/ vaccinations	-physical exam -diary reviewed and collected -assess all AEs, SAEs, NOCDs, AEs leading to withdrawal, ILI and AESIs -assess concomitant medications/ vaccinations -serology	-physical exam -assess all AEs, SAEs, NOCDs, AEs leading to withdrawal, ILI and AESIs -assess concomitant medications/ vaccinations

Adapted from BLA 125510/143, CSR 118_18, Table 6
*Message/phone call surveillance for ILI performed on weekly basis from Day 1 through Day 181 or end of regional influenza season, whichever was longer

6.1.8 Endpoints and Criteria for Study Success

Success Criterion for Primary Efficacy Objective

The primary efficacy objective was achieved if the lower limit (LL) of the two-sided 97.45% confidence interval (CI) of absolute vaccine efficacy (VE) estimate was > 0.4 using the primary protocol-definition of ILI.

Success Criteria for Secondary Immunogenicity Objectives

The endpoints of percent of subjects achieving seroconversion [defined as HI titer ≥1:40 for subjects seronegative at baseline (HI titer <1:10); or a minimum 4-fold increase in HI titer for subjects seropositive at baseline (HI titer ≥1:10) on Day 22] and HI titer ≥ 1:40 at Day 22 were assessed against the criteria described in CBER Guidance Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (2007):

- The LL of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 30%.
- The LL of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 60%.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The study was conducted across two influenza seasons. One interim analysis was performed. As a result, the 95% CIs were adjusted accordingly to reflect the interim analysis to control overall type I error under 5% for the final primary efficacy analyses. The subsequent strain-specific efficacy analyses were also carried out at the reduced alpha level as the primary efficacy analysis. The primary efficacy CIs were shown at 97.45% for the final analysis to reflect the adjustment for the interim analysis. Please refer to the statistical review for details.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

All Enrolled Set: All subjects who provided informed consent, received a subject identification number, and provided demographic and/or baseline screening information, regardless of randomization and treatment status in the study.

Exposed Set: All subjects in the All Enrolled Set who received study vaccination.

Full Analysis Set (FAS) Efficacy:
All enrolled subjects who were randomized and received a study treatment, were under observation for at least 21 days post-vaccination and provided efficacy data.

Full Analysis Set (FAS) Immunogenicity:
Randomly selected sample of 1702 subjects who were randomized, received a study treatment, and provided immunogenicity data at Days 1 and 22.

Per Protocol Set (PPS) for Efficacy/Immunogenicity:
Subjects who correctly received the vaccine, had no protocol deviation or other reasons leading to exclusion prior to unblinding.

Safety Set: Subjects who were exposed to the study vaccine and who provided safety data
− Solicited Safety Set: All subjects in the Exposed Set with any solicited AE data.
− Unsolicited Safety Set: All subjects in the Exposed Set with unsolicited AE data.
− Overall Safety Set: All subjects who were in the solicited safety set or in the unsolicited safety set.

6.1.10.1.1 Demographics

Overall, the demographic and baseline characteristics of subjects enrolled in this study were well balanced between the two vaccine groups.

Table 5: Demographics and Baseline Characteristics-All Enrolled Set

	aQIV (N=3392)	**Boostrix (N=3396)**	**Total (N=6790)**
Mean Age in Years (SD)	71.9 (5.53)	71.8 (5.36)	71.9 (5.44)
Age Group			
65 through 74 years	2416 (71.2%)	2406 (70.8%)	4822 (71.0%)
75 through 84 years	893 (26.3%)	928 (27.3%)	1821 (26.8%)
≥85 years	85 (2.5%)	62 (1.8%)	147 (2.2%)
Sex			
Male	1289 (38.0%)	1307 (38.5%)	2596 (38.2%)
Female	2105 (62.0%)	2089 (61.5%)	4194 (61.8%)
Ethnic Origin			
Hispanic or Latino	615 (18.1%)	607 (17.9%)	1222 (18.0%)
Not Hispanic or Latino	2773 (81.7%)	2779 (81.8%)	5552 (81.8%)
Race			
American Indian or Alaska Native	62 (1.8%)	59 (1.7%)	121 (1.8%)
Asian	1139 (33.6%)	1159 (34.1%)	2298 (33.8%)
Black or African American	1 (0.0%)	0	1 (0.0%)
White	1642 (48.4%)	1629 (48.0%)	3271 (48.2%)
Other	550 (16.2%)	549 (16.2%)	1099 (16.2%)
Mean Body Mass Index in kg/m^2 (SD)	27.05 (4.989)	26.96 (4.995)	27.00 (4.992)
Received Previous Seasonal Influenza Vaccine in the Past 5 Years	991 (29.2%)	1021 (30.1%)	2012 (29.6%)
Comorbidity Score[a]			
<50	2472 (72.8%)	2474 (72.9%)	4946 (72.8%)
≥50	922 (27.2%)	922 (27.1%)	1844 (27.2%)
Smoking Status			
Smoking	325 (9.6%)	335 (9.9%)	660 (9.7%)
Not Smoking	3069 (90.4%)	3061 (90.1%)	6130 (90.3%)

Adapted from BLA 125510/143, CSR 118_18, Table 15

[a]Score <50 is considered low risk for influenza-related complications and score ≥50 is considered high risk (17).

Reviewer comment: The demographics are reflective of the study sites and are not entirely representative of the US population. The previous vaccination rate of individuals 65 years of age and older in the US is likely to be higher compared to this study population.

6.1.10.1.3 Subject Disposition

Overall, 6790 subjects were enrolled in this study. Of these, 6761 (99.6%) subjects were exposed to study treatments with a similar number of subjects exposed to aQIV and Boostrix (3381received aQIV and 3380 received Boostrix). The proportion of subjects that discontinued the study was low (254 subjects [3.7%]) and balanced across the study treatment arms. The disposition of subjects is presented in the table below.

Table 6: Study Disposition

	aQIV	Boostrix	Total
Total Enrolled	3394	3396	6790
Total Exposed	3381 (99.6%)	3380 (99.5%)	6761 (99.6%)
Completed Protocol	3263 (96.1%)	3273 (96.4%)	6536 (96.3%)
Discontinued from Study	131 (3.9%)	123 (3.6%)	254 (3.7%)
Reason for Discontinuation			
Adverse Event	3 (0.1%)	3 (0.1%)	6 (0.1%)
Death	33 (1.0%)	34 (1.0%)	67 (1.0%)
Withdrawal by Subject	66 (1.9%)	61 (1.8%)	127 (1.9%)
Lost to Follow-up	21 (0.6%)	19 (0.6%)	40 (0.6%)
Protocol Deviation	6 (0.2%)	5 (0.1%)	11 (0.2%)
Other	2 (0.1%)	1 (0.0%)	3 (0.0%)

Adapted from BLA 125510/143, CSR 118_18, Table 10, 12, 36
Two subjects had missing treatment codes and were excluded from all exposed set

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Immunogenicity

Immunogenicity of aQIV was studied as a secondary objective as measured by hemagglutination inhibition (HI) titers 21 days after vaccination. The FAS immunogenicity subset consisted of 1656 subjects (1324 in the aQIV group and 322 in the Boostrix group).

Table 7: Number (%) of Subjects with HI Titers ≥1:40 and Seroconversion at Day 22 (FAS Immunogenicity)

HI≥1:40 (95% CI)	aQIV (N=1324)	Boostrix (N=322)
A/H1N1	96.2% (**95.05**, 97.18)	46.7% (41.18, 52.21)
A/H3N2	95.6% (**94.37**, 96.66)	41.7% (36.32, 47.21)
B/Yamagata	79.2% (**76.95**, 81.40%)	21.5% (16.93, 26.02)
B/Victoria	81.6% (**79.39**, 83.65)	18.4% (14.40, 23.03)
Seroconversion (95% CI)		
A/H1N1	78.0% (**75.66**, 80.21)	2.1% (0.85, 4.31)
A/H3N2	84.6% (**82.52**, 86.49)	3.9% (2.11, 6.62)
B/Yamagata	60.8% (**58.06**, 63.41)	3.6% (1.89, 6.27)
B/Victoria	65.5% (**62.88**, 68.10)	2.1% (0.85, 4.31)

Adapted from BLA 125510/143, CSR 118_18, Table 34, 35
Bold=Met CBER criteria. CBER criteria is achieved if the LL of the 2-sided 95% CI for % of subjects with HI≥1:40 met or exceeded 60% and if the LL of the 2-sided 95% CI for the % of subjects achieving seroconversion met or exceeded 30%. Seroconversion is defined as HI titer ≥1:40 for subjects seronegative at baseline (HI titer <1:10); or a minimum 4-fold increase in HI titer for subjects seropositive at baseline (HI titer ≥1:10) on Day 22.

Reviewer comment: The criteria for demonstrating immunogenicity under Accelerated Approval regulations, as described in the FDA Guidance for Industry, Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines, were met for all 4 strains by percentage of subjects with post-vaccination HI titer ≥ 1:40 and by seroconversion rates. Both the percentage of subjects with post-vaccination HI titer ≥1:40 and seroconversion rates were lower for the two B strains compared to the A strains.

6.1.11.2 Subpopulation Analyses

There were no notable subgroup differences in the immunogenicity of aQIV observed by age, comorbidity score, previous vaccination, sex, and race. While some subgroups showed higher or lower response compared to others, the CIs around the point estimates were generally overlapping.

Table 8: Subgroup Analyses of Percentage of Subjects with Post-vaccination HI≥1:40 and Seroconversion in Subjects Receiving aQIV (FAS Immunogenicity)

Strain	Subgroup	N	HI≥1:40 (95% CI)	Seroconversion (95% CI)
A/H1N1	Age 65 to <75 years	924	96.5 (95.1, 97.6)	79.6 (76.9, 82.2)
	Age 75 to <85 years	364	96.2 (93.6, 97.9)	75.0 (70.2, 79.4)
	Age ≥85 years	36	88.9 (73.9, 96.9)	66.7 (49.0, 81.4)
	Comorbidity score <50	878	96.8 (95.4, 97.9)	80.1 (77.3, 82.7)
	Comorbidity score ≥50	446	95.1 (92.6, 96.9)	73.9 (69.6, 78.0)
	No previous influenza vaccination[1]	931	95.5 (94.0, 96.7)	84.8 (82.3, 87.1)
	Previous influenza vaccination	393	98.0 (96.0, 99.1)	61.8 (56.8, 66.6)
	Female	775	96.6 (95.1, 97.8)	80.3 (77.3, 83.1)
	Male	549	95.6 (93.6, 97.2)	74.7 (70.9, 78.3)
	Asian	140	99.3 (96.1, 100.0)	75.9 (67.9, 82.8)
	White	1182	95.9 (94.6, 96.9)	78.2 (75.7, 80.5)
A/H3N2	Age 65 to <75 years	924	94.7 (93.1, 96.1)	84.4 (81.9, 86.7)
	Age 75 to <85 years	364	98.4 (96.5, 99.4)	85.4 (81.4, 88.9)
	Age ≥85 years	36	91.7 (77.5, 98.3)	80.6 (64.0, 91.8)
	Comorbidity score <50	878	95.3 (93.7, 96.6)	85.2 (82.7, 87.5)
	Comorbidity score ≥50	446	96.2 (94.0, 97.8)	83.4 (79.6, 86.7)
	No previous influenza vaccination	931	95.4 (93.8, 96.6)	89.9 (87.8, 91.8)
	Previous influenza vaccination	393	96.2 (93.8, 97.9)	71.9 (67.2, 76.3)
	Female	775	95.4 (93.6, 96.7)	85.1 (82.4, 87.6)
	Male	549	96.0 (94.0, 97.5)	83.8 (80.4, 86.8)
	Asian	140	98.6 (94.9, 99.8)	80.0 (61.7, 77.5)
	White	1182	95.3 (93.9, 96.4)	86.3 (84.2, 88.2)
B/Yamagata	Age 65 to <75 years	924	78.2 (75.3, 80.8)	62.4 (59.2, 65.6)
	Age 75 to <85 years	364	81.6 (77.2, 85.4)	56.5 (51.2, 61.6)
	Age ≥85 years	36	83.3 (67.2, 93.6)	61.1 (43.5, 76.9)
	Comorbidity score <50	878	80.4 (77.7, 83.0)	63.5 (60.2, 66.7)
	Comorbidity score ≥50	446	76.9 (72.7, 80.7)	55.4 (50.7, 60.1)
	No previous influenza vaccination	931	80.4 (77.7, 82.9)	65.9 (62.8, 69.0)
	Previous influenza vaccination	393	76.5 (72.0, 80.6)	48.5 (43.4, 53.6)
	Female	775	81.4 (78.5, 84.1)	63.2 (59.7, 66.7)
	Male	549	76.1 (72.3, 79.7)	57.2 (53.0, 61.4)
	Asian	140	82.0 (74.6, 88.0)	63.0 (54.2, 71.1)
	White	1182	78.9 (76.4, 81.2)	60.4 (57.6, 63.3)
B/Victoria	Age 65 to <75 years	924	80.8 (78.1, 83.3)	67.2 (64.1, 70.3)
	Age 75 to <85 years	364	83.7 (79.5, 87.4)	62.3 (57.1, 67.3)
	Age ≥85 years	36	80.6 (64.0, 91.8)	55.6 (38.1, 72.1)
	Comorbidity score <50	878	81.0 (78.3, 83.6)	67.4 (64.2, 70.5)
	Comorbidity score ≥50	446	82.7 (78.9, 86.1)	61.8 (57.1, 66.3)
	No previous influenza vaccination	931	83.5 (81.0, 85.9)	71.9 (68.9, 74.8)
	Previous influenza vaccination	393	77.0 (72.5, 81.0)	50.3 (45.2, 55.3)
	Female	775	80.5 (77.5, 83.2)	66.1 (62.6, 69.4)
	Male	549	83.2 (79.8, 86.2)	64.8 (60.6, 68.8)
	Asian	140	83.5 (76.2, 89.2)	67.7 (59.0, 75.5)
	White	1182	81.3 (79.0, 83.5)	65.2 (62.4, 67.9)

Adapted from BLA 125510/143, CSR 118_18, Table 14.2.1.2.1-5, 14.2.1.3.1-5
[1]Previous influenza vaccination in past 5 years

Reviewer comment: CBER immunogenicity criteria was met for each subgroup for each strain contained in the vaccine. The percentage of subjects achieving seroconversion in the subgroup of those who had received previous influenza vaccination within the past 5 years was consistently lower for each vaccine strain compared to that of subjects who were not previously vaccinated, but this difference was minimal for percentage with HI≥1:40. One possible explanation for this finding could be that it is harder to achieve a four-fold rise in HI titers, to meet the definition of seroconversion, in subjects with pre-existing high titers due to previous vaccination.

6.1.11.3 Dropouts and/or Discontinuations

Compared to the FAS immunogenicity set, the per-protocol set (PPS) for immunogenicity excluded an additional 76 subjects (68 in the aQIV group and 8 in the Boostrix group) due to protocol deviations. The most common reasons for exclusion were due to serum sample obtained outside window (40 in aQIV, 7 in Boostrix), positive influenza swab prior to Visit 3 (12 in aQIV, 1 in Boostrix), and subject did not meet the inclusion/exclusion criteria but the study vaccines were given (12 in aQIV, 0 in Boostrix) Analyses using the PPS for immunogenicity yielded similar results to those above.

Reviewer comment: There was an imbalance in protocol deviations between the two groups (5.1% aQIV group, 2.1% in Boostrix group). However, there was no notable difference in immunogenicity results with exclusion of data from these subjects.

6.1.11.4 Other Analyses

The primary objective of this study was to demonstrate the absolute vaccine efficacy (VE) of aQIV versus a non-influenza comparator (Boostrix). The VE against RT-PCR confirmed influenza due to any strain was 19.80% and the LL of the 97.45% CI was -5.27%. The study failed the pre-specified success criteria of LL of the 97.45% CI of VE against any strain >40%.

Table 9: Vaccine Efficacy for RT-PCR Confirmed Influenza (Any Strain and by Strain)- Protocol-defined ILI (FAS Efficacy)

	aQIV N=3368		**Boostrix N=3372**		**Adjusted VE (%) (97.45% CI)**
Strain	Cases	Attack Rate (%)	Cases	Attack Rate (%)	
Any strain	122	3.6	151	4.5	19.80 (-5.27, 38.91)
(b) (4)					

Adapted from BLA 125510/143, CSR 118_18, Table 19
*B strain represents B/Yamagata and B/Victoria

The 2016-2017 NH and 2017 SH seasons during which the study was conducted were driven by A/H3N2. Specifically, 96 of 122 (79%) influenza cases in the aQIV arm, and 118 of 151 (78%) influenza cases in the Boostrix arm were A/H3N2 subtype. A large percentage of circulating strains were mismatched to the vaccine strain. As seen in the table below, only 7 of 58 (12%) of culture-confirmed cases in the aQIV arm were antigenically matched, and the remaining 51 of 58 (88%) of cases were mismatched.

The same trend was observed in the Boostrix arm as well [14 of 81 cases (17%) matched vs. 67 of 81 cases (83%) mismatched].

Table 10: Number of Vaccine Matched and Vaccine Unmatched Culture-Confirmed Cases

	Strains	**aQIV N=3368**	**Boostrix M=3372**
Vaccine Matched	Any	7	14
	H1N1	1	0
	H3N2	4	8
	B/Yamagata	2	6
	B/Victoria	0	0
Vaccine Unmatched	Any	51	67
	H1N1	0	0
	H3N2	47	65
	B*	4	2

Adapted from BLA 125510/143, CSR 118_18, Table 21, 25
*B strain represents B/Yamagata and B/Victoria

Reviewer comment: Although the study failed to meet its pre-specified success criteria for efficacy, the majority of the influenza cases found during the study were A/H3N2 that were mismatched to the vaccine strain. Overall vaccine effectiveness may not be able to be concluded based on results from these 2 seasons in this study alone. It is possible that vaccine efficacy may be greater in a season when there is a greater match between the circulating strains and the strains contained within the vaccine. Clinical endpoint efficacy will still need to be demonstrated by the Applicant in a future confirmatory efficacy study.

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety analysis was conducted on the Solicited Safety Set which included 1332 vaccinated subjects including 665 and 667 subjects, respectively, in the aQIV and Boostrix arms. All vaccinated subjects were observed for at least 30 minutes post vaccination on Day 1 for immediate reactions. Solicited local and systemic adverse reactions (ARs) that may have occurred post vaccination from Day 1 through Day 7 were recorded by subjects in the provided subject Diary. For all subjects, any unsolicited AE and concomitant medication use, after vaccination from Day 1 to Day 22 were collected at the Day 15 safety phone call and during the Day 22 clinic visit. During the remaining follow-up phase of the study (up to Day 366), safety data including AEs leading to withdrawal, AESI, NOCD and SAE and concomitant medication use related to these events were captured via safety phone calls or clinic visits. Additionally, a safety follow-up call was to be made 30 days after an ILI onset to determine if subsequent medically attended AEs occurred.

6.1.12.2 Overview of Adverse Events

<u>Solicited Adverse Reactions</u>

Table 11: Number (%) of Subjects with Local Solicited Adverse Reactions from Day 1 Through Day 7 After Vaccination (Solicited Safety Set)

	Grade	aQIV (N[1]=665) n[2]/M[3] (%)	Boostrix (N=667) n/M (%)
Pain	Any	102/624 (16.3%)	71/632 (11.2%)
	Severe	2/624 (0.3%)	2/632 (0.3%)
Erythema	Any ≥25 mm	23/600 (3.8%)	11/607 (1.8%)
	Severe (>100 mm)	0	3/607 (0.5%)
Induration	Any ≥25 mm	24/603 (4.0%)	16/611 (2.6%)
	Severe (>100 mm)	1/603 (0.2%)	2/611 (0.3%)
Ecchymosis	Any ≥25 mm	3/595 (0.5%)	4/607 (0.7%)
	Severe (>100 mm)	0	0

Adapted from BLA 125510/143, CSR 118_18, Table 39
[1]N=total number of subjects
[2]n=number of subjects per group
[3]M=number of subjects with available data for the relevant endpoint

There was a slightly higher rate of local solicited ARs observed after administration of aQIV compared to Boostrix. No difference in the rates of severe local solicited ARs were observed between the two groups.

Table 12: Number (%) of Subjects with Systemic Solicited Adverse Reactions from Day 1 Through Day 7 After Vaccination (Solicited Safety Set)

	Grade	aQIV (N[1]=665) n[2]/M[3] (%)	Boostrix (N=667) n/M (%)
Headache	Any	69/640 (10.8%)	53/640 (8.3%)
	Severe	5/640 (0.8%)	3/640 (0.5%)
Fatigue	Any	67/640 (10.5%)	56/640 (8.8%)
	Severe	7/640 (1.1%)	3/640 (0.5%)
Myalgia	Any	49/640 (7.7%)	39/640 (6.1%)
	Severe	5/640 (0.8%)	3/640 (0.5%)
Arthralgia	Any	47/641 (7.3%)	42/640 (6.6%)
	Severe	4/641 (0.6%)	4/640 (0.6%)
Chills	Any	32/639 (5.0%)	25/641 (3.9%)
	Severe	3/639 (0.5%)	2/641 (0.3%)
Diarrhea	Any	26/640 (4.1%)	19/638 (3.0%)
	Severe	3/640 (0.5%)	2/638 (0.3%)
Nausea	Any	24/638 (3.8%)	15/640 (2.3%)
	Severe	1/638 (0.2%)	1/640 (0.2%)
Loss of Appetite	Any	23/638 (3.6%)	23/639 (3.6%)
	Severe	0	2/639 (0.3%)
Fever	Any ≥38.0° C	11/659 (1.7%)	8/664 (1.3%)
	≥40° C	0	0
Vomiting	Any	5/638 (0.8%)	7/640 (1.1%)
	Severe	1/638 (0.2%)	1/640 (0.2%)

Adapted from BLA 125510/143, CSR 118_18, Table 40
[1]N=total number of subjects
[2]n=number of subjects per group
[3]M=number of subjects with available data for the relevant endpoint
Severe arthralgia, chills, fatigue, headache, myalgia, and nausea=prevents daily activity; severe loss of appetite=not eating at all; severe vomiting=6 or more times in 24 hours or requires intravenous hydration; severe diarrhea= 6 or more loose stools in 24 hours or requires intravenous hydration.

The most frequently reported systemic solicited ARs in >10% of subjects in either the aQIV or Boostrix groups were headache (10.8% and 8.3% in aQIV and Boostrix arms

respectively) and fatigue (10.5% and 8.8% in aQIV and Boostrix arms respectively). Severe systemic solicited ARs were uncommon in both vaccine groups and varied from 0% to 1.1% of subjects in the aQIV group, and from 0.2% to 0.6% of subjects in the Boostrix group. Overall, the rate of any solicited systemic AR was slightly higher in the aQIV group compared to the Boostrix group.

Reviewer comment: The slightly higher rate of solicited local and systemic ARs in the aQIV group compared to Boostrix is not unexpected given aQIV is an adjuvanted vaccine, and thus is expected to be more reactogenic. Importantly, there does not appear to be a difference in the incidence of severe ARs between the two groups.

Unsolicited Adverse Events

The proportion of subjects with unsolicited AEs during the treatment period were similar between the vaccine groups (21.5% in aQIV group and 21.2% in Boostrix group). Overall, 0.6% of subjects in the aQIV group and 0.4% in the Boostrix group experienced unsolicited AEs during the treatment period that were considered severe in intensity. The proportion of subjects with unsolicited AEs that were assessed as at least possibly related to the study vaccine were similar between the aQIV and Boostrix groups (9.0% and 7.7%, respectively). Related unsolicited AE reported by >1% of subjects in either group consist of injection site pain (1.7% in aQIV and 1.6% in Boostrix) and ILI (1.5% in aQIV and 1.4% in Boostrix).

6.1.12.3 Deaths

There were 33 deaths (1.0%) in the aQIV group and 34 deaths (1.0%) in the Boostrix group during the study. None of the deaths were assessed by the investigators to be related to the study treatments. The majority of the deaths (11/33 in the aQIV group and 16/34 in the Boostrix group) were due to unsolicited AEs belonging to the SOC Cardiac disorders.

Reviewer comment: Narratives of the deaths were reviewed and the reviewer concurs with the investigator's assessments that the deaths were unrelated to the study vaccines. The number and percentage of deaths during the study are not unexpected given the study population of older subjects, some with co-morbidities.

6.1.12.4 Nonfatal Serious Adverse Events

Overall, 238 (7.0%) subjects in the aQIV group and 234 (6.9%) subjects in the Boostrix group experienced at least one SAE. SAEs were most frequently reported in the SOCs Infections and infestations (57 [1.7%] subjects and 55 [1.6%] subjects, respectively); Cardiac disorders (56 [1.7%] subjects and 67 [2.0%] subjects, respectively); and Nervous system disorders (37 [1.1%] and 34 [1.0%] subjects, respectively). The most frequently reported SAEs by PT were pneumonia (19 [0.6%] aQIV and 18 [0.5%] Boostrix), chronic obstructive pulmonary disease (12 [0.4%] aQIV and 14 [0.4%] Boostrix) and acute myocardial infarction (12 [0.4%] aQIV and 19 [0.6%] Boostrix).

Only one subject in the aQIV group experienced a SAE (rheumatoid arthritis requiring hospitalization), also listed as AESI, that was considered possibly related to study

treatments by the investigator. The case was not considered to be related to the study treatment by the Applicant.

Reviewer comment: Narrative of SAE and AESI for subject (b) (6) *was reviewed. Briefly, subject is a 68 year old white male with medical history of dyslipidemia on atorvastatin who was randomized to receive aQIV. Subject experienced ILI 48 days after vaccination with aQIV, which resolved after 4 days. Over the following few months, the subject complained intermittently of symptoms in the hands and fingers (initially swelling and stiffness, then tingling, then changed to pain without swelling or stiffness). The subject was hospitalized 217 days after vaccination for symptoms of joint pain and swelling, and diagnosed with rheumatoid arthritis (RA) (verbatim term: rheumatoid polyarthritis seronegative) and started on treatment. He was found to be rheumatoid factor and cyclic citrullinated peptides negative on workup. This event was judged by the investigator to be an SAE (due to hospitalization) and an AESI that is possibly related to the study vaccine. The Applicant judged this event to be unrelated to the study vaccine due to timing of events. In the opinion of this reviewer, there is nothing remarkable in the history which suggests that this event was likely related to the study vaccine. Symptoms appeared to have started shortly after the ILI episode, so a viral etiology could also be a possible trigger for this potential case of autoimmune disease. It is also unclear how certain this diagnosis of RA was given the negative markers on testing. Regardless, background cases of RA or other arthritic disease would not be unusual for the subject population included in this study. This reviewer concurs with the judgment of the Applicant that the event is likely to be unrelated to the study vaccine.*

6.1.12.5 Adverse Events of Special Interest (AESI)

Four subjects (0.1%) in the aQIV group and 6 (0.2%) subjects in the Boostrix group experienced AEs that were considered AESIs. The AESIs experienced by subjects were considered not related to study treatment; except one AESI, rheumatoid arthritis, experienced by a subject in the aQIV group which was considered possibly related by the investigator, but unrelated by the Applicant (see above section for narrative).

6.1.12.7 Dropouts and/or Discontinuations

The proportion of subjects who experienced any unsolicited AE that led to premature withdrawal was similar in the aQIV and Boostrix groups (37 [1.1%] subjects and 36 [1.1%] subjects, respectively). The AEs leading to premature withdrawal were most frequently reported in the SOC Cardiac Disorders for both vaccine groups (11 [0.3%] and 16 [0.5%] subjects, respectively). One subject in the aQIV group reported pyrexia at Day 24 which led to premature withdrawal from study and was assessed as possibly related.

Reviewer comment: In the opinion of this reviewer, it is unlikely that the pyrexia in this subject was an adverse reaction related to the study vaccine, given the onset of fever was more than 3 weeks after vaccination.

6.1.12.8 Subpopulation Analyses

Subgroup analyses of safety, including solicited ARs through Day 7, unsolicited AEs through day 22, SAEs, deaths and AESIs through the entire study period, by age (65 through <75 years and ≥ 75 years), sex and race did not reveal any imbalance between the aQIV group and Boostrix group.

6.1.13 Study Summary and Conclusions

Immunogenicity results from study V118_18 demonstrate that Fluad Quadrivalent was able to meet CBER criteria based on percentage of subjects with HI titers ≥1:40 and percentage of subjects with seroconversion for all 4 strains contained in the vaccine. These HI antibody responses serve as surrogate endpoints reasonably likely to predict benefit. The study failed to meet the pre-specified success criteria for vaccine efficacy against any RT-PCR confirmed influenza. However, A/H3N2 that was unmatched to the strain contained in the vaccine accounted for a majority of influenza cases in the study. Thus, clinical efficacy of the vaccine cannot be concluded based on results from this single study. The rates of solicited adverse reactions were slightly higher with Fluad Quadrivalent compared to Boostrix; however, the rates of severe solicited ARs were comparable between the two groups. There were no notable differences in the rates of unsolicited reactions, SAEs, or deaths. Overall, the results from this study are sufficient to support accelerated approval of Fluad Quadrivalent.

6.2 V118_20

Study V118_20 serves to provide additional supportive safety data for Fluad Quadrivalent. Study V118_20 was a phase 3, randomized, double-blind, controlled, multicenter, clinical study to evaluate safety and immunogenicity of an MF59-adjuvanted quadrivalent subunit influenza vaccine in comparison with an M59-adjuvanted trivalent subunit influenza vaccine and an MF59-adjuvanted trivalent subunit influenza vaccine containing the alternate B strain, in adults ages 65 years and older.

6.2.1 Objectives

Co-primary immunogenicity objectives:

1. To demonstrate that vaccination with aQIV elicits an HI antibody response that is not inferior to that of an aTIV containing the same virus strains as the licensed adjuvanted influenza vaccine (FLUAD aTIV-1), and an aTIV containing the alternate B strain (aTIV-2) among adults ≥65 years of age.
2. To assess the immunogenicity of aQIV in adults ≥65 years of age based on the CBER immunogenicity criteria.

Safety objective:
To assess the safety and tolerability of aQIV, aTIV-1, and aTIV-2 among adults ≥65 years of age.

6.2.2 Design Overview

The study enrolled 1778 male and female adults ≥65 years of age who were healthy or had co-morbidities. Subjects were randomized to 2:1:1 to receive one dose of aQIV, aTIV-1, or aTIV-2 and were subsequently followed for safety for 6 months. Immune response was measured on Day 1 and Day 22. Solicited local and systemic adverse events were monitored for 7 days after vaccination. Unsolicited AEs were monitored for 21 days following vaccination. Serious adverse events, AEs leading to withdrawal from

the study, new onset of chronic diseases, and AEs of special interest were followed for the full duration of the study.

6.2.3 Population

Inclusion Criteria:
Males and females ≥65 years old who were healthy or had comorbidities

Exclusion Criteria:

1. History of behavioral or cognitive impairment or psychiatric condition that, in the opinion of the Investigator, may have interfered with the subject's ability to participate in the study
2. History of any medical condition considered an AESI
3. Progressive or severe neurological disorder, seizure disorder, or history of Guillain-Barré syndrome
4. Hypersensitivity, including allergy, to any component of vaccines, medicinal products, or medical equipment whose use was foreseen in this study
5. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws, including bleeding diathesis, or any other condition that may have been associated with prolonged bleeding
6. Abnormal function of the immune system resulting from:
    a. Clinical conditions affecting the immune system (e.g., HIV infection, agammaglobulinemia)
    b. Systemic administration of corticosteroids (PO/IV/IM) at a dose equivalent to 20 mg/day of prednisone for more than 14 consecutive days within 90 days prior to informed consent
    c. Administration of antineoplastic and immunomodulating agents (e.g., TNF-α antagonists or anti-B cell antibodies) or radiotherapy within 1 year prior to informed consent
7. Receipt of immunoglobulins or any blood products within 180 days prior to informed consent
8. Receipt of an investigational or nonregistered medicinal product within 30 days prior to informed consent or before completion of the safety follow-up period in another study, or who are unwilling to refuse participation in another clinical study at any time during the conduct of this study (note: concomitant participation in an observational study not involving drugs, vaccines, or medical devices, is acceptable)
9. Study personnel or immediate family members (brother, sister, child, parent), the spouse of personnel with direct involvement in the study
10. Receipt of any influenza vaccine within 6 months prior to enrollment in this study, or plan to receive influenza vaccine prior to the Day 22 blood collection
11. Receipt of any inactivated non-influenza vaccine 14 days or live-attenuated vaccine 28 days prior to enrollment in this study or plans to receive any other non- influenza vaccine within 28 days from study vaccination
12. Fever at the time of screening, defined as oral temperature ≥38.0 degrees Celsius (≥100.4° F). Enrollment could be considered if fever is absent for 72 hours
13. Signs or symptoms of acute infection at the time of screening. Enrollment could be deferred if signs and symptoms are absent for 72 hours
14. Fatal prognosis of an underlying medical condition (<12 months life expectancy)

15. Any other clinical condition that, in the opinion of the Investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.

Reviewer comment: Eligibility criteria were appropriate for this study and allow for generalizability to a US population of adults 65 years of age and older.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Table 13: Composition of aQIV, aTIV-1, and aTIV-2 in V118_20

Ingredients	**aQIV** Quantity Per Dose	**aTIV-1** Quantity per dose	**aTIV-2** Quantity per dose	Function
Active Ingredients Hemagglutinin (HA) and Neuraminidase (NA) antigens from the influenza virus strains:				Active ingredient
A/Singapore/GP1908/2015 IVR-180 (H1N1)	15 mcg	15 mcg	15 mcg	
A/Hong Kong/4801/X-263B (H3N2)	15 mcg	15 mcg	15 mcg	
B/Brisbane/9/2014 (Yamagata)	15 mcg	-	15 mcg	
B/Brisbane/60/2008 (Victoria)	15 mcg	15 mcg	-	
Adjuvant				
Squalene	9.75 mg	9.75 mg	9.75 mg	Oil phase
Polysorbate 80	1.175 mg	1.175 mg	1.175 mg	Surfactant
Sorbitan trioleate	1.175 mg	1.175 mg	1.175 mg	Surfactant
Sodium citrate	0.66 mg	0.66 mg	0.66 mg	Buffer
Citric acid	0.04 mg	0.04 mg	0.04 mg	Buffer
Other Ingredients				
(b) (4)				
Water for injection	Up to 0.50 mL	Up to 0.50 mL	Up to 0.50 mL	Diluent

Adapted from BLA 125510/143, CSR 118_20, Table 2

Each vaccine is administered as a single 0.5mL intramuscular dose into the deltoid muscle.

6.2.6 Sites and Centers

The study was conducted in 20 study centers in the United States.

6.2.7 Surveillance/Monitoring

Table 14: Time and Events V118_20

Study Day	1	3	15	22	91, 181
Assessment	-Informed consent -Medical history -Physical exam -Vitals -Eligibility -Serology -Vaccine administered -Study supplies and instructions -Assess ILI -Assess SAEs, NOCDs, withdrawal AEs, AESIs, and associated medications	-Telephone contact -Assess ILI -Assess SAEs, NOCDs, withdrawal AEs, AESIs, and associated medications	-Telephone contact -Assess ILI -Assess all unsolicited AEs and concomitant medications -Assess SAEs, NOCDs, withdrawal AEs, AESIs, and associated medications	-Physical exam -Serology -Diary card reviewed -Assess ILI -Assess unsolicited AEs and concomitant medications -Assess SAEs, NOCDs, withdrawal AEs, AESIs, and associated medications	-Telephone contact -Assess SAEs, NOCDs, withdrawal AEs, AESIs, and associated medications

Adapted from BLA 125510/143, CSR 118_20, Table 3

6.2.8 Endpoints and Criteria for Study Success

The aQIV was considered to be noninferior to aTIV-1, containing the same virus strains as the licensed adjuvanted trivalent influenza vaccine, and aTIV-2, containing the alternate B strain if, for each of the 4 strains, the following statistical criteria are met:

- The upper bound of the two-sided 95% confidence interval (CI) for the ratio of the HI antibody GMTs (GMTr) did not exceed 1.5. The HI antibody GMTr was calculated as GMTaTIV/GMTaQIV; and
- The upper bound of the two-sided 95% CI for the difference between the HI antibody SCRs did not exceed 10%. The difference in SCRs was calculated as SCR SCRaTIV–SCRaQIV.

The second co-primary immunogenicity objective for aQIV was assessed 21 days after vaccine administration by applying CBER criteria for the elderly population for each of the 4 strains included in aQIV. The endpoints for percentage of subjects vaccinated with aQIV achieving seroconversion and HI titer ≥1:40 at Day 22 was assessed against the criteria described in CBER Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (CBER/FDA 2007):

- The lower bound of the two-sided 95% confidence interval for the percentage of subjects achieving seroconversion for HI antibody should have met or exceeded 30%.
- The lower bound of the two-sided 95% confidence interval for the percentage of subjects achieving an HI antibody titer ≥1:40 should have met or exceeded 60%.

6.2.9 Statistical Considerations & Statistical Analysis Plan

See statistical review for full details.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

All Enrolled Set: All subjects who provided informed consent, received a subject identification number, and provided demographic and/or baseline screening information, regardless of randomization and treatment status in the study.

Exposed Set: All subjects in the All Enrolled Set who received study vaccination.

Full Analysis Set (FAS) Immunogenicity: All subjects in the All Enrolled Set who were randomized, received at least 1 study vaccination, and provided immunogenicity data at Day 1 and Day 22.

Per Protocol Set (PPS) Immunogenicity: All subjects in the FAS Immunogenicity who did not have any major protocol deviations that were assessed as potentially impacting on immunogenicity results.

Safety Set: All subjects in the Exposed Set who received at least 1 dose or a partial dose of study vaccine and provided any evaluable follow-up safety data
− Solicited Safety Set: All subjects in the Exposed Set with any solicited AE data.
− Unsolicited Safety Set: All subjects in the Exposed Set with unsolicited AE data.
− Overall Safety Set: All subjects who were in the solicited safety set or in the unsolicited safety set.

6.2.10.1.1 Demographics

There were no notable differences observed in the baseline characteristics and demographics across vaccine groups.

Table 15: Summary of Demographics and Baseline Characteristics (All Enrolled Set)

	aQIV N=889	aTIV-1 N=445	aTIV-2 N=444	Total N=1778
Mean age in years (SD)	72.4 (5.54)	72.4 (5.60)	72.6 (5.46)	72.5 (5.53)
% Male	41.8%	44%	45.7%	43.4%
Race				
White	91.6%	90.6%	92.6%	91.6%
Black or African American	6.6%	8.3%	6.5%	7.0%
Asian	1.0%	0.4%	0.2%	0.7%
Native Hawaiian or Pacific Islander	0.1%	0.2%	0	0.1%
American Indian or Alaska Native	0.6%	0	0.5%	0.4%
Other	0.1%	0.4%	0.2%	0.2%
Ethnicity				
Hispanic or Latino	6.6%	8.3%	7.0%	7.1%
Not Hispanic or Latino	93.0%	91.7%	92.3%	92.5%
BMI (kg/m^2)				
Mean (SD)	29.60 (6.157)	29.79 (5.858)	29.69 (5.647)	29.67 (5.956)
Previous Influenza Vaccination, n (%)	760 (85.5%)	380 (85.4%)	401 (90.3%)	1541 (86.7%)
Mean Total Risk Score[a] (Comorbidity) (SD)	46.0 (33.50)	44.6 (30.25)	46.5 (34.15)	45.8 (32.88)

Adapted from BLA 125510/143, CSR 118_20, Table 8

[a]Score <50 is considered low risk for influenza-related complications and score ≥50 is considered high risk (17).

Reviewer comment: The study included predominantly Caucasian population and is not entirely reflective of total US population.

6.2.10.1.3 Subject Disposition

The vast majority of subjects who were exposed to the study vaccine was able to complete the study.

Table 16: Disposition of Subjects-Age at Enrollment (All Enrolled Set)

	aQIV	**aTIV-1**	**aTIV-2**	**Overall**
All enrolled set	889	445	444	1778
Exposed set	888 (99.9%)	444 (99.8%)	444 (100%)	1776 (99.9%)
Completed the study	881 (99.1%)	440 (98.9%)	439 (98.9%)	1760 (99.0%)
Safety set	888 (99.9%)	444 (99.8%)	444 (100%)	1776 (99.9%)
FAS Immunogenicity	886 (99.7%)	443 (99.6%)	441 (99.3%)	1770 (99.6%)
PPS Immunogenicity	872 (98.1%)	436 (98.0%)	433 (97.5%)	1741 (97.9%)
Reasons for early discontinuation				
Adverse event	0	0	0	0
Withdrawal of consent	1 (0.1%)	1 (0.2%)	1 (0.2%)	3 (0.2%)
Lost to follow-up	5 (0.6%)	4 (0.9%)	4 (0.9%)	13 (0.7%)
Protocol deviation	0	0	0	0
Death	2 (0.2%)	0	0	2 (0.1%)

Adapted from BLA 125510/143, CSR 118_20, Table 4

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Analysis of the first co-primary endpoint shows that Fluad Quadrivalent was able to meet the pre-specified noninferiority criteria against aTIV-1 and aTIV-2 as measured by HI GMTR and difference in seroconversion 22 days after vaccination.

Table 17: Analyses of Noninferiority of aQIV Relative to aTIVs as Measured by HI GMTR and Difference in HI Seroconversion Rates 22 Days Postvaccination (PPS)

Strain	**aQIV N=872**	**aTIV-1 N=433**	**aTIV-2 N=433**	**aTIV pooled N=869**	**GMT ratio (aTIV/aQIV) and 95% CI**
A/H1N1	65.01	-	-	75.16	1.16 (1.05, **1.27**)
A/H3N2	294.91	-	-	293.31	0.99 (0.90, **1.09**)
B/Yamagata	24.67	-	24.30		0.99 (0.90, **1.08**)
B/Victoria	30.78	30.13	-		0.98 (0.89, **1.08**)
					SCR Difference (aTIV-aQIV) and 95% CI
A/H1N1	35.21	39.45	37.41		3.23 (-1.30, **7.76**)
A/H3N2	39.33	39.70	37.18		0.37 (-4.23, **4.96**)
B/Yamagata	16.40	-	15.47		-0.93 (-5.13, **3.27**)
B/Victoria	13.42	12.16	-		-1.26 (-5.07, **2.55**)

Adapted from BLA 125510/143, CSR 118_20, Table 9, 10
Bold=met noninferiority criteria.
Noninferiority criterion for the GMT ratio: the upper bound of the two-sided 95% CI on the ratio of GMT (aTIV/aQIV) should not have exceeded 1.5.
Noninferiority criterion for the SCR difference: the upper bound of the two-sided 95% CI on the difference between SCRs aTIV–aQIV should not have exceeded 10%.

Fluad Quadrivalent was not able to meet the second co-primary endpoint using CBER immunogenicity criteria based on percentage of subjects with HI titer $\geq$1:40 and percentage of subjects with seroconversion for either B strain.

Table 18: Number (%) of Subjects with HI Titers $\geq$1:40 and Seroconversion at Day 22 (PPS)

HI$\geq$1:40 (95% CI)	**aQIV (N=872)**	**aTIV-1/aTIV-2* (N=869)**
A/H1N1	69.38 (**66.20**, 72.43)	70.31 (**67.15**, 73.33)
A/H3N2	93.92 (**92.12**, 95.41)	94.82 (**93.13**, 96.20)
B/Yamagata	32.80 (29.69, 36.03)	36.95 (32.39, 41.69)
B/Victoria	38.19 (34.95, 41.51)	36.95 (32.38, 41.65)
Seroconversion (95% CI)		
A/H1N1	35.21 (**32.03**, 38.48)	38.43 (**35.19**, 41.76)
A/H3N2	39.33 (**36.08**, 42.67)	39.70 (**36.43**, 43.04)
B/Yamagata	16.40 (14.0, 19.03)	15.47 (12.20, 19.23)
B/Victoria	13.42 (11.22, 15.86)	12.16 (9.24, 15.60)

Adapted from BLA 125510/143, CSR 118_20, Table 11
Bold=Met CBER criteria. CBER criteria is achieved if the LL of the 2-sided 95% CI for % of subjects with HI$\geq$1:40 met or exceeded 60% and if the LL of the 2-sided 95% CI for the % of subjects achieving seroconversion met or exceeded 30%. Seroconversion is defined as HI titer $\geq$1:40 for subjects seronegative at baseline (HI titer <1:10); or a minimum 4-fold increase in HI titer for subjects seropositive at baseline (HI titer $\geq$1:10) on Day 22.
*aTIV-1 and aTIV-2 groups were pooled for the analysis of A-H1N1 and A/H3N2 strains. For B/Victoria TV=aTIV-1, for B/Yamagata TIV=aTIV-2.

Reviewer comment: Fluad Quadrivalent, along with both aTIVs included in the study failed to meet CBER immunogenicity criteria for the B strains. These results are

somewhat unexpected given Fluad (aTIV-1 in this study) was licensed based on immunogenicity data demonstrating that it was able to meet these criteria in previous studies. Study V118_18 also had immunogenicity data which showed adequate immune response for the B strains for aQIV. In response to a CBER IR regarding these results, the Applicant proposed that these results were due to inter-laboratory variability, which was concluded by the CBER CMC review team to be a plausible explanation. See regulatory history section for further details. This reviewer proposes that another possible explanation for these results is that it may be harder to generate an adequate level of response in a highly immunized population (as was the case in this study) compared to a more vaccine-naïve population (as was the case for V118_18). In particular, subjects who have been previously vaccinated but remain seronegative at baseline or with low baseline HI titers may be individuals who respond less robustly to influenza vaccines. Although the immunogenicity results from this study are difficult to interpret, as Fluad is already licensed and marketed for use, and there is no evidence to suggest that aQIV is less immunogenic compared to aTIV, it would benefit the US population from a public health perspective to make available the quadrivalent formulation, which has the potential to protect against two B strains instead of only one. The Applicant will still need to demonstrate clinical endpoint efficacy in a future study.

6.2.11.5 Exploratory and Post Hoc Analyses

The Applicant proposed that the lower immunogenicity results observed in this study are likely due to inter-laboratory variability. Re-testing of a subset of samples from V118_20 under the V118_18 protocol showed that there was a substantial increase in GMT and percentage of subjects with HI titers$\geq$1:40 compared to the results in the CSR, but CBER criteria based on percentage of subjects with seroconversion were still not met.

Reviewer comment: The results from the reanalysis of V118_20 samples are reassuring that inter-laboratory variability may in part explain the poor immunogenicity results observed in this study. However, as these re-analyses were post-hoc and since immunogenicity results from V118_20 will not be featured in product labeling, these results will not be discussed in detail in this review. Further information regarding the post-hoc study design and results can be found in the regulatory history section of this review as well as the CMC review.

6.2.12 Safety Analyses

6.2.12.1 Methods

Subjects were followed for solicited local and systemic adverse reactions (ARs) for 7 days after vaccination (Day 1 to Day 7), unsolicited AEs for 21 days after vaccination (Day 1 to Day 22), and SAEs, AEs leading to withdrawal from the study, NOCDs, AESIs, and concomitant medications associated with these events as collected from Day 1 to Day 181.

6.2.12.2 Overview of Adverse Events

Solicited Adverse Reactions

Table 19: Summary of Local Solicited Adverse Reactions Through Day 7 (Solicited Safety Set)

Symptom	**aQIV (N[1]=883) n[2]/M[3] (%)**	**aTIV-1 (N=439) n/M (%)**	**aTIV-2 (N=438) n/M (%)**
Pain			
Any	274/860 (31.8%)	123/423 (29.1%)	108/420 (25.7%)
Severe	0	4/423 (0.9%)	1/420 (0.2%)
Erythema			
Any ≥25mm	61/801 (7.6%)	29/391 (7.4%)	34/397 (8.6%)
Severe (>100mm)	0	1/391 (0.3%)	0
Induration			
Any ≥25mm	56/803 (7.0%)	21/390 (5.4%)	21/397 (5.3%)
Severe (>100mm)	0	0	0
Ecchymosis			
Any ≥25mm	20/794 (2.5%)	6/392 (1.5%)	6/392 (1.5%)
Severe (>100mm)	1/794 (0.1%)	0	0

Adapted from BLA 125510/143, CSR 118_20, Table 23
[1]N=total number of subjects
[2]n=number of subjects per group
[3]M=number of subjects with available data for the relevant endpoint

The observed rates of solicited local ARs were slightly higher in the aQIV group compared to the aTIV groups. No significant differences in rates of severe solicited local ARs were observed across aQIV and aTIV groups.

Reviewer comment: For erythema, induration, and ecchymosis, the Applicant classified a reaction 0 to 24mm as one category. Thus, rate of no reactions or rate of reactions between 0 to <25mm is unknown. The slightly higher rate of solicited local AEs in aQIV compared to aTIV is not unexpected given the higher antigen content. The rates of solicited local ARs appear to be higher in this study compared to those seen with aQIV in study V118_18. However, the rates of severe solicited local ARs remain low at 0.1% or less for each reaction.

Table 20: Summary of Solicited Systemic ARs through Day 7 (Solicited Safety Set)

Symptom	**aQIV (N^1=883) n^2/M^3 (%)**	**aTIV-1 (N=439) n/M**	**aTIV-2 (N=438) n/M**
Fatigue			
Any	140/876 (16%)	67/435 (15.4%)	50/434 (11.5%)
Severe	6/876 (0.7%)	3/435 (0.7%)	6/434 (1.4%)
Headache			
Any	105/875 (12%)	46/435 (10.6%)	49/434 (11.3%)
Severe	4/875 (0.5%)	3/435 (0.7%)	3/434 (0.7%)
Arthralgia			
Any	80/876 (9.1%)	37/435 (8.5%)	31/434 (7.1%)
Severe	3/876 (0.3%)	0	5/434 (1.2%)
Myalgia			
Any	71/875 (8.1%)	34/436 (7.8%)	30/434 (6.9%)
Severe	4/875 (0.5%)	0	4/434 (0.9%)
Diarrhea			
Any	48/875 (5.5%)	24/435 (5.5%)	30/434 (6.9%)
Severe	5/875 (0.6%)	2/435 (0.5%)	3/434 (0.7%)
Chills			
Any	41/875 (4.7%)	15/435 (3.4%)	19/434 (4.4%)
Severe	2/875 (0.2%)	2/435 (0.5%)	3/434 (0.7%)
Nausea			
Any	35/875 (4.0%)	18/436 (4.1%)	20/434 (4.6%)
Severe	2/875 (0.2%)	0	4/434 (0.9%)
Loss of Appetite			
Any	28/877 (3.2%)	21/435 (4.8%)	16/434 (3.7%)
Severe	2/877 (0.2%)	0	2/434 (0.5%)
Vomiting			
Any	7/875 (0.8%)	2/435 (0.5%)	9/434 (2.1%)
Severe	1/875 (0.1%)	0	3/434 (0.7%)
Fever			
≥38° C	4/882 (0.5%)	1/439 (0.2%)	2/438 (0.5%)
≥40° C	0	0	0

Adapted from BLA 125510/143, CSR 118_20, Table 24

[1]N=total number of subjects

[2]n=number of subjects per group

[3]M=number of subjects with available data for the relevant endpoint

Severe arthralgia, chills, fatigue, headache, myalgia, and nausea=prevents daily activity; severe loss of appetite=not eating at all; severe vomiting=6 or more times in 24 hours or requires intravenous hydration; severe diarrhea= 6 or more loose stools in 24 hours or requires intravenous hydration.

No remarkable differences overall in rates of individual systemic solicited ARs were observed across the aQIV and the aTIV groups.

Unsolicited AEs

The rates of unsolicited treatment emergent AEs were similar across the 3 vaccine groups (19.8% aQIV, 17.1%, aTIV-1, and 20.5% aTIV-2). Severe unsolicited AEs were reported by 3%, 5.2%, and 2.7% of subjects in the aQIV, aTIV-1, and aTIV-2 groups, respectively. The rates of unsolicited AEs that were assessed as related to the study vaccine were similar between aQIV and the 2 aTIV vaccine groups (4.4% aQIV, 3.8% aTIV-1, and 4.3% aTIV-2 groups). Injection site bruising (1.0% aQIV, 1.1% aTIV-1, 1.4% aTIV-2) was the only related unsolicited AE reported by >1% of subjects in any group.

6.2.12.3 Deaths

Two deaths occurred during the study in the aQIV group: one death of a 72 year old female with multiple comorbidities who died of unknown cause 3.5 months after vaccination and one death of a 72 year old male who died of unknown causes approximately 3 months after vaccination. Both deaths were considered by the investigator to be unrelated to the study vaccine.

Reviewer comment: Narratives of the two deaths were reviewed. Although there were some similarities between the two cases (both subjects 72 years old, both died approximately 3 months after vaccination, and both died of unknown causes), there were no features in the cases to suggest these events were related to the study vaccine. No autopsy was performed on the subjects to ascertain exact cause of death. Given the age of the subject population, and existing comorbidities, it is not unexpected to capture cases of deaths during study follow up. This reviewer concurs with the findings of the investigators that the deaths were unlikely to be related to the study vaccine.

6.2.12.4 Nonfatal Serious Adverse Events

Overall, 83 (4.7%) subjects reported at least one SAE during the study period; the rates of SAEs were generally similar across the vaccine groups (4.2% aQIV group, 6.3% aTIV-1, and 4.1% in aTIV-2). No SAEs were reported to be related to any of the study vaccines. No SAEs lead to subject withdrawal from the study in any vaccine group.

6.2.12.5 Adverse Events of Special Interest (AESI)

Two subjects experienced 1 AESI each in the study. One subject in the aTIV-1 group had Addison's disease and one subject in the aQIV group had polymyalgia rheumatica. Both were considered by the Investigator to be unrelated to the study vaccines.

6.2.13 Study Summary and Conclusions

Overall, the safety profile of aQIV was acceptable and comparable with aTIV. There was a slightly higher rate of solicited local adverse reactions in subjects who received aQIV as compared to those who received aTIV. The rates of solicited systemic ARs, unsolicited adverse events, and SAEs were similar between aQIV and aTIV. Solicited ARs were observed at a higher rate in aQIV in this study compared to study V118_18, but the rates of severe reactions remained similarly low. Study V118_20 did not meet both of its pre-specified co-primary immunogenicity endpoints of demonstration of non-inferiority of aQIV versus aTIV-1 and aTIV-2 based on GMTR and seroconversion and meeting CBER criteria based on percentage of subjects with HI titer $\geq$1:40 and percentage of subjects with seroconversion. Inter-laboratory variability may have impacted the immunogenicity results observed and thus make the immunogenicity data difficult to interpret.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No pregnancies were reported in these studies as they were conducted in an older adult population. There are insufficient data to establish the safety of Fluad Quadrivalent in pregnant women.

9.1.2 Use During Lactation

No data were reported regarding use during lactation in these studies which were conducted in an older adult population.

9.1.3 Pediatric Use and PREA Considerations

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups must be submitted at the time an application for a new active ingredient is submitted, unless the requirement for assessment has been deferred or waived.

A partial waiver for conducting studies with aQIV in children from birth to <6 months of age was granted because the necessary studies are impossible or highly impracticable to conduct in this age group [Section 505B(a)(4)(i)]. In children <6 months of age, a clinical endpoint study would be necessary to support licensure, because the association between hemagglutination inhibition (HI) titer and protection from influenza is not well-established in this age group and the presence of maternal antibodies would confound the interpretation of immunogenicity data without relying on clinical endpoints to assess efficacy. An efficacy study would be impracticable due to considerations such as need for large sample size, timely recruitment of infants in this age cohort, and the logistics of administering 2 doses of vaccine early in the influenza season in order to assess for efficacy during the remainder of season.

A deferral was granted for children 6 months to <72 months of age [Section 505B(a)(3)]. A partial waiver was granted for children 6 years to <17 years of age because the product does not represent at meaningful therapeutic benefit over existing therapies for patients in that age group and is not likely to be used by a substantial number of pediatric patients in that age group [Section 505B(a)(5)(B)(iii))]. Fluad Quadrivalent does not represent a meaningful therapeutic benefit over Seqirus's existing influenza vaccines approved for use in this age group (Afluria in children ≥ 6 months, Fluvirin in children ≥ 4 years, and Flucelvax in children ≥ 4 years).

9.1.4 Immunocompromised Patients

The immune response to Fluad Quadrivalent in immunocompromised persons was not evaluated for this supplement. The immune response in immunocompromised individuals, including those receiving immunosuppressive therapy, may be lower than in immunocompetent individuals.

9.1.5 Geriatric Use

Fluad Quadrivalent has been studied and is intended for adults 65 years of age or older for active immunization against influenza disease caused by influenza virus subtypes A and B contained in the vaccine.

10. CONCLUSIONS

The clinical data submitted in this supplement support the safety and effectiveness of Fluad Quadrivalent in persons 65 years of age and older. The clinical recommendation is for accelerated approval, based on meeting immunogenicity criteria in study V118_18 as outlined in FDA's Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines. The overall safety profile of Fluad Quadrivalent is comparable to Fluad and is acceptable for approval.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 21: Summary of Risk-Benefit Consideration for Fluad Quadrivalent

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• During the past influenza season (2018-2019), an estimated 531,000 to 647,000 hospitalizations and 36,000 to 61,200 deaths were related to influenza disease. • An estimated 50 to 70 percent of influenza hospitalizations occur in adults 65 years of age and older • An estimated 70 to 90 percent of influenza deaths occur in adults 65 years of age and older.	• Influenza is a major cause of morbidity and mortality in the US. • A substantial proportion of infections result in serious or life-threatening disease, particularly among high-risk groups such as the elderly
Unmet Medical Need	• Older adults have decreased immunologic responsiveness to currently available influenza vaccines than younger adults. • Currently, 5 licensed, standard dose, quadrivalent, inactivated influenza vaccines, one high dose, quadrivalent, inactivated influenza vaccine, and one quadrivalent, recombinant influenza vaccine are available to adults 65 years of age and older. However, immune responses to standard-dose seasonal influenza vaccination is lower in this population.	• In adults 65 years of age and older, there is an unmet medical need for highly effective prevention of influenza infection caused by the 4 strains of influenza recommended for inclusion in quadrivalent formulations of the vaccine.
Clinical Benefit	• One clinical trial in adults 65 years of age and older conducted under IND (V118_18) demonstrated that Fluad Quadrivalent was able to meet CBER immunogenicity criteria based on percentage of subjects with HI titers $\geq$1:40 and percentage of subjects with seroconversion at Day 22. This study failed to meet the pre-specified efficacy success criteria; however, this study was conducted during seasons with high antigenic mismatch between the circulating strains and the strains contained in the vaccine.	• Use of HI titers is an acceptable surrogate marker reasonably likely to demonstrate clinical benefit as required for accelerated approval the immunogenicity results from V118_18 fulfill this requirement. • Prevention of influenza illness in the elderly reduces morbidity and mortality associated with influenza infection in adults 65 years of age and older.
Risk	• The most substantial risks of vaccination with Fluad Quadrivalent were mild local and systemic reactogenicity. • No other safety signals, including no notable imbalances in unsolicited AEs, SAEs, deaths, and AESIs, were apparent in evaluation of the safety data from V118_18 and V118_20	• All the evidence indicates that the risk of vaccination with Fluad Quadrivalent is acceptable
Risk Management	• The package insert lists the most common risks of vaccination with Fluad Quadrivalent (occurring in > 10% of subjects). These are: injection site pain, fatigue, and headache. However, only a small proportion of these local and systemic injection site reactions were severe in intensity and all resolved without sequelae.	• The package insert and the current pharmacovigilance plan would be adequate to manage these risks.

11.2 Risk-Benefit Summary and Assessment

Data submitted to the BLA establish a substantial likelihood of benefit for prevention of RT-PCR-confirmed influenza caused by any influenza viral type/subtype included in the vaccine. As the risks of vaccination with Fluad Quadrivalent in adults 65 years of age and older have been found to be minimal, in association with a substantial likelihood of benefit in the prevention of influenza disease caused by vaccine types/subtypes contained in the vaccine, the overall risk-benefit profile of this product is determined to be favorable.

11.3 Discussion of Regulatory Options

Per accelerated approval regulations (21 CFR§601.41), licensure is based on a surrogate marker that is reasonably likely to predict clinical benefit for products that provide a meaningful therapeutic benefit to patients over existing treatments. Providing prophylaxis to the elderly population, who are at higher risk for influenza related complications and for whom there is lower vaccine efficacy for available influenza vaccines compared to younger adults, provides a meaningful benefit over the existing treatments. Study V118_18 evaluated safety and immunogenicity using HI titers as a surrogate for protection and had an appropriate trial design to support accelerated approval. Study V118_20 provided safety data that support an acceptable safety profile of aQIV. Demonstration of clinical effectiveness is required post licensure and will be evaluated in a proposed confirmatory efficacy trial V118_24.

11.4 Recommendations on Regulatory Actions

Fluad Quadrivalent is recommended for accelerated approval, based on the surrogate of HI titer, for active immunization of adults 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

11.5 Labeling Review and Recommendations

Revisions to the package insert were communicated to the Applicant. The main changes to the package insert were the descriptions and results of the clinical studies. Minor edits were also done to maintain consistency with the Fluad (aTIV) label.

11.6 Recommendations on Postmarketing Actions

No changes to the submitted pharmacovigilance plan for Fluad Quadrivalent are recommended based on the information contained in this Application. Under the accelerated approval regulations, a confirmatory efficacy trial is required to verify and describe the clinical benefit of Fluad Quadrivalent. The Applicant has proposed V118_24, an absolute efficacy trial comparing Fluad Quadrivalent to a non-influenza comparator vaccine in adults $\geq$65 years of age. The final study protocol has not been submitted for review by CBER at the time of approval.