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Application Type	Biologics License Application
STN	125510/0
CBER Received Date	25 November 2014
PDUFA Goal Date	25 November 2015
Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name(s)	Sarah K. Browne, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Roshan Ramanathan, MD, MPH
	Jeff Roberts, MD
Applicant	Novartis Vaccines and Diagnostics, Inc.
Established Name	Influenza Vaccine, Adjuvanted
(Proposed) Trade Name	Fluad®
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	**Antigens (≥15 µg hemagglutinin per strain):** A/California/7/2009 (H1N1)-like A/Perth/16/2009 (H3N2)-like B/Brisbane/60/2008-like **Adjuvant (MF-59):** Squalene (9.75 mg) Polysorbate 80 (1.175 mg) Sorbitan trioleate (1.175 mg) Sodium citrate (b) (4) (0.66 mg) Citric acid (0.04 mg) **Excipients** (b) (4)
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 is an inactivated influenza vaccine proposed for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. Fluad 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
aTIV	adjuvanted trivalent influenza vaccine
BLA	biologics license application
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CMC	chemistry, manufacturing, and controls
EMA	European Medicines Authority
FAS	full analysis set
GMT	geometric mean titer
HA	hemagglutination antigen
HAI	hemagglutination antigen inhibition
ILI	Influenza-Like Illness
IM	Intramuscular
ISS	integrated summary of safety
LB	lower bound
MedDRA	medical dictionary for regulatory activities
NOCD	new-onset of chronic disease
OBE	Office of Biostatistics and Epidemiology
PeRC	Pediatric Review Committee (CDER)
PPS	per protocol set
PREA	Pediatric Research Equity Act
RCT	randomized controlled trials
SAE	serious adverse event
SOC	system organ class
SOP	standardized operating procedure
TIV	trivalent Influenza Vaccine

1. Executive Summary

A Biologics License Application (BLA) was submitted by Novartis Vaccines and Diagnostics (NVD, the Applicant) to the Food and Drug Administration (FDA) for an adjuvanted seasonal trivalent influenza virus vaccine (Fluad). The candidate vaccine includes a proprietary adjuvant, MF59C.1 and influenza antigens (total dose of 45 micrograms HA) that are produced in eggs using the Agriflu manufacturing process. The proposed indication is for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine in persons 65 years of age and older.

The BLA includes immunogenicity and safety data from one phase 3 clinical trial conducted in adults $\geq$ 65 years of age (study V70_27), which was designed to provide data to support licensure under the accelerated approval pathway. A confirmatory efficacy trial is required under the accelerated approval regulations to verify and describe the clinical benefit of Fluad and has been proposed by the Applicant. Trial V118_18 is an absolute efficacy trial comparing an MF59 adjuvanted quadrivalent inactivated seasonal influenza vaccine (aQIV) produced using the Agriflu manufacturing process with an active control Tdap vaccine, (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed [Boostrix®]), in adults $\geq$ 65 years of age.

With regard to inclusion of an adjuvant in the vaccine formulation, from a regulatory perspective, there is the requirement for the adjuvanted vaccine formulation, as for any vaccine, to be demonstrated as both safe and effective, with a favorable benefit-risk evaluation, but there is no explicit requirement for demonstrating the safety and effectiveness of the adjuvanted vaccine formulation in comparative clinical trials using adjuvanted and unadjuvanted vaccine formulations.

Study V70_27 was a randomized, active-controlled, observer-blind, multicenter clinical trial that compared the safety and immunogenicity of Fluad to Agriflu (an unadjuvanted trivalent inactivated influenza subunit vaccine licensed in the U.S.) in subjects $\geq$ 65 years of age. Subjects were randomly allocated in a 1:1:1:3 ratio to receive one of three lots of Fluad (N = 3552) or Agriflu (N= 3552). The primary immunogenicity objectives to be analyzed in a stepwise fashion were lot-to-lot consistency, noninferiority, and then superiority of Fluad over Agriflu for homologous strains. Criteria for equivalence had to be met in order for the data from the 3 lots to be pooled for the non-inferiority analyses. Non-inferiority criteria were met if the lower bound of the 95% confidence interval for the difference in seroconversion rates (Fluad-Agriflu) and geometric mean titers (GMT) ratios (Fluad: Agriflu) were > -10% and > 0.67, respectively. Superiority criteria were met if the lower bound of the 95% confidence interval for the difference in seroconversion rates (Fluad-Agriflu) and GMT ratios (Fluad: Agriflu) were >10% and > 1.5, respectively for at least two of the three strains. The pre-specified criteria for demonstration of equivalency of three lots of Fluad and noninferiority of immunogenicity relative to Agriflu were met. Immunologic superiority of Fluad compared to Agriflu was demonstrated for only one of the three influenza vaccine strains (H3N2) and therefore was not met.

Fluad was associated with increased solicited local and systemic reactogenicity compared to Agriflu within the 7 Day post-vaccination period (48% versus 35%, respectively), but rates of

grade 3/severe adverse events (AEs) were balanced between arms for both solicited local and systemic reactions and comprised ≤ 1% of subjects across all categories. The percentage of unsolicited AEs through Day 22 postvaccination was 16% in both groups; 4% in Fluad versus 5% in Agriflu were considered by the investigator to be related. Four serious adverse events (SAEs) were assessed to be possibly or probably related to the study vaccination: 1 SAE (bronchitis, presented Day 8) in the Fluad group and 3 SAEs (asthmatic crisis [presented Day 13], chronic obstructive pulmonary disease [presented Day 63], and Guillain-Barré syndrome [presented Day 227]) in the Agriflu group. There were no deaths within 21 Days of vaccine administration. Deaths occurring during the 1 year study duration were reported in similar proportions in both the Fluad and Agriflu arms: 1.5% and 1.3%, respectively. One death was considered related to the study vaccination, a death attributed to Guillain-Barré Syndrome in a subject who received Agriflu.

Data from an additional 49 supportive studies, conducted in adults ≥ 65 years of age between 1992 and 2013 (N=27,787) were submitted to the BLA. These studies evaluated 4 different formulations of a MF59 adjuvanted product and were small and highly varied in design (e.g., uncontrolled, open-label, non-randomized, and/or using comparators that were not licensed in the US). Thus, the purpose of submitting these data was to provide a larger safety database. NVD and the Center for Biologics Evaluation and Research (CBER) agreed prior to submission of the BLA that immunogenicity data from these studies would not be reviewed or included in labeling because antibody response may vary by strains included in the vaccine, there were differences in the assays used and the laboratory conducting the assays, and the assays were not adequately validated. Review of pooled safety analyses from these studies showed a similar safety profile to that observed in the above referenced pivotal trial V70_27 and did not reveal safety concerns.

Product, assay and clinical statistical reviews supported approval of the licensure application. There were no important lot-release or site inspection issues identified.

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting convened on September 15, 2015 to review and discuss the safety and immunogenicity data derived from studies conducted with Fluad and submitted in the BLA. The committee was asked to vote and voted affirmatively that the available data support the safety and effectiveness of Fluad for the proposed indication via the accelerated approval pathway.

The Pediatric Research Equity Act (PREA) required that we consider the utility of studying Fluad in Pediatric age groups 0 through 16 years of age. A partial waiver was granted for those ages 9 through 16 with the rationale based on Section 505B(a)(4)(B)(iii) of the Federal Food Drug and Cosmetic Act: the drug or biological product—(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is not likely to be used by a substantial number of pediatric patients in that age group. A deferral was granted for ages 0 through 8 years for which one study has been completed, one study is ongoing and two are proposed. CBER has requested that the completed safety and immunogenicity study in infants and toddlers ages 6 to 72 months of age be submitted with the efficacy supplement with the data from the ongoing relative efficacy study in the same age group (anticipated for April 2019). The remaining two proposed studies will be performed in 0

to 6 months of age and 6 to 8 years of age, the data for which are anticipated in February of 2023 for both.

The routine pharmacovigilance monitoring plan is adequate. Confirmatory efficacy trial V118_18 is a postmarketing requirement (PMR) under the accelerated approval regulations. No additional postmarketing commitments (PMCs) or PMRs are deemed necessary at this time.

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

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Review of demographic data for subjects in study V70_27 revealed a well-balanced distribution between study arms with overall percentages of 36% male, 53% Asian, 28% Caucasian, 18% Hispanic, 1% Black and < 1% each Other, Native American, Alaskan, Pacific Islander, and Hawaiian. Because 70% of subjects were enrolled outside of the United States, the demographic distribution of subjects in this study is influenced by that of those countries and is less reflective of the demographics solely within the United States. Subgroup analyses revealed no important differences in safety or effectiveness based on race or ethnicity. Although GMT ratios and seroconversion rates were higher in women than men, they were proportionally higher in both treatment arms such that the point estimates and 95% confidence intervals for both GMT ratios and seroconversion rate differences were similar by gender.

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 250,000 to 500,000 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). 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 (3, 4). During the past 4 influenza seasons 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 (3, 4). Adults ≥ 65 years of age also account for the majority (90%) of deaths from seasonal influenza in the United States (3, 4).

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

Currently, four FDA-licensed antiviral drugs are available for use in the United States (Tamiflu®, Relenza®, Symmetrel® and Flumadine®). Of these, only the neuraminidase inhibitors Tamiflu and Relenza are currently recommended for use by the Centers for Disease Control and Prevention. Use of adamantine class derivatives (Symmetrel and Flumadine) is no longer recommended

because many strains of influenza, including the 2009 H1N1 influenza, are now 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 (5) with most of the benefit derived when given prophylactically or early in the disease course. However, 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 have been commercially available since the 1940s. Currently, eight inactivated standard dose trivalent influenza vaccines (TIV) are licensed in the U.S for use in adults 65 years of age and older. These include Fluzone®, Flucelvax®, Fluvirin®, FluLaval®, Fluarix®, and Afluria®, Agriflu® and Flublok®. Three standard-dose, inactivated quadrivalent influenza vaccines are available for use in adults 65 years of age and older: Fluarix Quadrivalent®, FluLaval Quadrivalent®, and Fluzone Quadrivalent®. While standard dose trivalent and quadrivalent vaccines have been shown to be effective at preventing influenza infection in adults, specific data for older adults are limited to evaluation of immunogenicity. Fluzone High-Dose is currently the only licensed high-dose inactivated trivalent influenza vaccine available for use in adults 65 years of age and older and demonstrated superior immunogenicity and efficacy compared to standard dose Fluzone in the randomized clinical trials submitted to support this indication. Of note, none of the currently US licensed seasonal influenza vaccines contain an adjuvant.

In general, as demonstrated in trials evaluating immunogenicity of standard dose influenza vaccines, immune responses are substantially lower in adults $\geq$ 65 years of age, presumably due to decreased T-cell-dependent antibody responses, other systemic medical comorbidities, and functional disabilities (6). 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 $\geq$ 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. 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 (7).

For additional details regarding the safety and efficacy data to support each of the inactivated influenza products listed above, please refer to the package insert for each of these products, which can be retrieved at:
http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm.

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

Fluad was first registered in Italy in 1997 and is currently authorized in 38 countries including Canada, and 15 European countries through individualized regulatory authorities, but not through the centralized European Medicines Agency (EMA). It is indicated for active immunization against influenza in adults 65 years of age and older, with the exception of the Philippines, South Africa and Canada, where it is indicated for use in individuals $\geq$ 60 years of

age, individuals ≥ 12 years of age and children 6 months to < 2 years of age, respectively. It is estimated that approximately 85.1 million doses have been administered based on the most recent periodic safety report extending through April 30, 2015 that summarizes the cumulative experience since postmarketing data collection began on May 15, 1997. No safety signals have emerged.

On November 27, 2014, the Italian national regulatory agency (AIFA) suspended two batches of Fluad as a precautionary measure when a small number of deaths occurred in elderly patients who had received Fluad. On December 12, 2014, a press release issues by the EMA indicated that testing of the batches and review of the case reports by the EMA and the AIFA did not reveal a causal link between the fatal events and Fluad administration (8), and the suspension was lifted.

Effectiveness of Fluad has been suggested in case-control and open-label observational studies (9, 10, 11), but efficacy has not been established in a prospective, randomized, controlled trial.

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

Pre-Submission

On December 18, 2009 the Applicant submitted a pre-IND briefing packet to CBER which included a synopsis for the planned phase 3 trial V70_27 intended to support licensure of Fluad in elderly adults in the United States. On March 2, 2010 CBER provided a response to the questions submitted by the Applicant which was followed by a conference call between CBER and the Applicant on March 3, 2010. These exchanges established concurrence between CBER and the Applicant regarding the requirements for a future BLA submission:

- The dose of adjuvant and antigen present in the current formulation of Fluad was acceptable for use in the proposed studies
- The Applicant acknowledged understanding that accelerated approval is granted for a new vaccine only if there is a shortage of influenza vaccine for the US market at the time of approval per "Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines". Concurrence was also reached regarding criteria for immunologic noninferiority and superiority based on this guidance document as well.
- The Applicant was informed that the proposed phase 3 Trial V70_27 would support accelerated approval of Fluad and that "traditional approval would require a clinical endpoint study with virus culture confirmation in subjects 65 years of age and older. This study should be designed to be observer-blind, randomized and controlled using the prevention of influenza illness as the primary endpoint." CBER suggested that an absolute efficacy study may be conducted as a confirmatory trial unless the Applicant was pursuing a claim of superiority for which a relative efficacy study would be required. The Applicant submitted an absolute efficacy study V118_18 which was reviewed by CBER.

Post-submission

Review of the standardized operating procedure (SOP) used to measure HAI titers revealed that what the Applicant defined as (b) (4) starting dilution was what CBER viewed as a (b) (4) starting dilution. This discrepancy would impact which subjects were categorized as seronegative (HAI

titer < 1:10) and which subjects achieved seroconversion (HAI titer ≥ 1:40 in subjects with a baseline titer of <1:10; four-fold increase for subjects with a baseline HAI titer ≥ 1:10). In post-submission communications, the Applicant agreed to rectify this by dividing the reported titers by a factor of 2 and based on those data recalculate the number of individuals who were seronegative and who met criteria for seroconversion, and revise the figures and tables in the clinical study report accordingly. A complete revised version 2 of the clinical study report were received by CBER on May 19th, 2015.

A total of 28 amendments were submitted in response to CBER information requests. Amendments 3, 4, 8, 9, 11, 14, 15, 16, 20, 21, 27, and 28, along with an email response sent by the applicant on 11 September 2015, had relevance to the clinical review. These amendments satisfactorily addressed all clinical information requests sent during the review period and have been incorporated into this Memorandum.

Reviewer comment: As expected, recalculation of the HAI titers resulted in more subjects being defined at baseline as seronegative for each homologous strain. However, the relative percentages of subjects who were seronegative at baseline remained balanced between groups and the overall GMT ratios comparing Day 1 to Day 22 titers did not change appreciably since both the values (e.g., numerator and denominator) were divided by 2.

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 difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Thirty eight sites participated, including 21 sites (30% of subjects) in the United States, 11 sites (52% of subjects) in the Philippines, 4 sites (14% of subjects) in Colombia, and 2 sites (3% of subjects) in Panama. Three sites were audited, one foreign and two U.S. clinical investigator study sites, representing 11% of total subjects enrolled. The inspections revealed no issues that would impact the data submitted in this BLA. For full details please refer to the Bioresearch Monitoring Final Discipline Review Memo dated August 31, 2015.

3.3 Financial Disclosures

Financial disclosures are outlined in Tables 1 and 2. No conflicts are noted.

Table 1. Financial Disclosures for the Phase 3 Study Submitted as the Basis for Licensure.

Covered clinical study (name and/or number): V70_27 NCT01162122: A Phase III, Randomized, Controlled, Observer-Blind, Multicenter Study to Evaluate the Safety and Immunogenicity and the Consistency of Three Consecutive Lots of a MF59C.1 Adjuvanted Trivalent Subunit Influenza Vaccine in Elderly Subjects Aged 65 Years and Older		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 266
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

Table 2. Financial Disclosures for Supportive Studies Supplying Additional Safety Data

Covered clinical studies (name and/or number): V104P3; V7P3; V7P5; V7P6; V7P7; V7P8; V7P17; V7P25; V7P26; M63P1; V7P6 V7P24; V7P26; V7P27; V7P30; V7P34		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 59		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 (of those identified via efforts at due diligence).		

Reviewer comment: The financial disclosures for the supportive studies were included in one financial disclosure form and are supplying safety data only. The Applicant reports due diligence in their effort to identify and contact all known investigators from each trial.

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

4.1 Chemistry, Manufacturing, and Controls

A complete review of the chemistry, manufacturing, and controls (CMC) data submitted to this BLA was conducted by the Division of Viral Products. The review focused on the fact that this product will be the first influenza vaccine where protein antigen purified from influenza virus is formulated with MF59 adjuvant during manufacturing process as opposed to mixing prior to injection. Therefore, the manufacturing process, specifications, and testing of the Fluad vaccine Final Bulk and Final Filled container are different from specifications used to characterize vaccines that contain only antigen. The review additionally evaluated and confirmed that introduction of the adjuvant did not affect potency or stability

4.2 Assay Validation

Please see the bioassay statistical review from the Office of Biostatistics and Epidemiology for full details. This review focused on the HAI assay and Single Radial Immunodiffusion (SRID) assay. The HAI assay, performed by (b) (4) for the phase 3 trial V70_27, used the (b) (4) instead of the traditional starting dilution (b) (4) Since this was not consistent with how serum dilution is traditionally defined by CBER in this assay, and the comparability study was not felt to be applicable, the applicant, per CBER request, recalculated titers based on the (b) (4) serum dilution. Additionally, the SRID procedure was validated for the determination of HA of Agriflu final product. A study was conducted to verify the

applicability of the SRID assay to HA content determination of Fluad. It was noted that the intermediate precision assessment was conducted within a range of (b) (4) HA/mL, across strains and batches, which did not adequately cover the proposed assay range (b) (4) HA/mL). Nevertheless, the SRID assay was validated for Agriflu and the intermediate precision assessment was intended to verify applicability of the procedure. Thus, it was determined that the SRID assay was acceptable.

4.3 Nonclinical Pharmacology/Toxicology

Please see detailed toxicology review of studies including five general toxicology studies, four genotoxicology studies, and one reproductive toxicology study. The reviewer did not identify any safety issues from the general toxicology studies or evidence of genotoxicity. The reproductive toxicology studies did not raise safety concerns and were adequate to support a pregnancy category B classification.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vaccination against influenza results in an immune 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 (12). Because these studies were conducted in younger adults and used attenuated challenge viruses to assess protection, induction of HI titer > 1:40, has not been proven to correlate with protection of older adults from illness due to wild type influenza viruses (13). Indeed, vaccine failures have been described in association with high HI titers previously thought to be protective (14), 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 stabilized by the addition of two non-ionic surfactants (15). 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, this has yet to be linked directly to clinical effectiveness (16, 17).

4.5 Statistical

Please see the clinical statistical review verified the safety and immunogenicity data and conclusions submitted to this BLA. Of note, differences of <0.1 for GMT ratios and <1% for seroconversion rates and rate differences were noted between statistical immunogenicity evaluation by CBER and the data tables submitted to the BLA. Additionally, for the safety assessment, the statistical review evaluated data tables which excluded signs of local reactogenicity (e.g erythema, induration, swelling) that were between 1 and 25mm (see

reviewer comment on page 37 for similar discussion regarding the VRBPAC briefing document). For this reason, the values reported by the statistical review for any local reactogenicity and local for signs of reactogenicity which can be measured are lower than those reported in this review.

Reviewer comment: Each of these differences was evaluated in detail and do not impact the conclusions drawn for this product.

4.6 Pharmacovigilance

Based on discussions with the Applicant, the following postmarketing activities summarized below are described in the review submitted by the Office of Biostatistics and Epidemiology:

- Routine passive surveillance including; all adverse event reports and asymptomatic maladministration spontaneously reported or actively captured in post-marketing studies; global literature review; vaccine production and distribution reports; production of IND safety reports; and close monitoring for Bell's palsy, convulsion, demyelinating disorders, encephalitis, GBS, neuritis, vasculitis, vaccination failure, medication errors
- Enhanced surveillance to provide reporting of all serious and non-serious conditions associated with neurological and neuro-inflammatory disorders, musculoskeletal disorders, gastrointestinal inflammatory disorders, rheumatologic conditions, metabolic disorders, vasculitides, connective tissue disorders, autoimmune-mediated conditions, severe immediate allergic reactions," toxic skin reactions, narcolepsy, arthritis, rheumatologic diseases, and polymyalgia rheumatic, as 15-Day expedited reports to the Vaccine Adverse Event Reporting System (VAERS).
- Enhanced passive surveillance will be obtained by monitoring the first 1000 doses administered at participating sites in Italy or through November 24, whichever comes first. Vaccine recipients will be instructed to report adverse events occurring within 1 week of vaccination. They will be provided a call center number and a vaccination card with information on brand, batch number, and date of vaccine administration.

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

5.1 Review Strategy

A single phase 3 Study for both safety and efficacy (V70_27) was submitted to this BLA to serve as the primary basis for licensure for both immunogenicity and safety. In addition, pooled safety analyses from 49 non-IND clinical studies conducted overseas were included in the integrated summary of safety (ISS) as agreed upon between the Applicant and CBER. These studies were conducted between 1992 and 2013 evaluating 27,787 subjects who received either MF59 adjuvanted trivalent influenza vaccine (aTIV) or an unadjuvanted trivalent influenza vaccine (TIV). Data from these studies were provided to assess safety, but were not used to support immunogenicity due to limitations in study design, variations in vaccine formulations and testing, use of non-United States licensed comparators, and uncertain status of assay validation. Thus, phase 3 study V70_27 is described in detail in Section 6, whereas the 49 studies providing supportive safety data will be reviewed in the integrated overview of safety (Section 8).

The following subheadings will be deleted from the review for the following reasons:

- Section 7 Integrated Overview of Efficacy because only one study V70_27 evaluating immunogenicity, discussed in section 6.1, was submitted to provide evidence for efficacy.
- Section 8 Integrated Overview of Safety includes selected sections to address additional supportive studies submitted for the provision of additional safety data with emphasis on Deaths, SAEs, and Adverse Events of Special Interest (AESIs).

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 of STN 125510/0:

STN 125510 Sections

- 1.3 Financial Disclosures
- 1.14 Labeling
- 1.16 Risk Management Plans
- 5.2 Tabular Listing of All Clinical Studies

5.3.5.1: Studies

- The full clinical study report, safety and immunogenicity data for study V70_27
- Study report synopses and safety data for 14 randomized controlled trials in individuals ≥ 65 years of age receiving a single dose of Fluad or TIV: V7P3, V7P5, V7P6, V7P7, V7P8, V7P17, V7P24,V7P25, V7P26, V7P27, V7P30, V7P34, M63P1, V104P3
- Study report synopses and safety data from seventeen uncontrolled seasonal studies and four bridging or stability studies: V7P1S, V7P2S, V7P3S, V7P4S,V7P5S, V63P1S, V70P1S, V70P2S, V70P3S, V70P4S, V70P5S, V70P7S, V70_09S, V70_25S, V70_32S, V70_39S, V70_44S, V7P31, V7P32, V63P1, V70P1,
- Study report synopses and safety data from seven revaccination studies V7P3X1, V7P5X1, V7P7X1, V7P8X1, V7P25X1, V7P3X2, V7P5X2
- Study report synopsis and safety data from one Phase 4 study in elderly subjects: V7P35
- Study report synopses and safety data from five studies conducted in young adults: V7P9, V7P12, V7P15, V7P18, V7P38

5.3.5.3: Reports of Analyses from More than One Study

Amendments to this initial submission were reviewed as indicated in Section 2.5.

5.3 Table of Studies/Clinical Trials

Table 3. Summary of Study Submitted to BLA 125510/0 to Serve as Primary Basis for Licensure[1]

Study	Design	Control	Total Number of Subjects[3]	Age (years)	Countries (number of sites)
V70_27 NCT01162122	Randomized, observer-blind[2], multi-center phase 3	Agriflu	7104 (3552 each received Fluad or Agriflu)	65 years of age and older	United States (21), Philippines (11), Columbia (4), Panama (2)

[1]For review of additional studies submitted for provision of additional safety data please refer to Table 25, Section 8.2.1.

[2]Observer-blind meant that the unblinded qualified study member, independent of the safety evaluation and other study evaluations (including assessment of respiratory illness), administered the vaccine. The Investigators in charge of safety assessment and respiratory illness data collection did not know which product was administered. The subject did not know which product was administered.
[3]Number of randomized subjects; see subject disposition, Table 7.

5.4 Consultations

5.4.1 Advisory Committee Meeting

A Vaccines and Related Biologics Advisory Committee (VRBPAC) meeting was held on September 15, 2015. The Applicant and the Agency both provided their perspectives on the data that were submitted to this BLA. Two questions were posed to the committee at the outset and are listed below along with the results of the voting that occurred at the close of the meeting.

1. Are the immunogenicity data adequate to support the effectiveness of Fluad under the accelerated approval regulation for the prevention of influenza disease in adults 65 years of age and older?
   Voting results: eleven committee members voted "yes", one voted "no" and one abstained.

2. Are the available data adequate to support the safety of Fluad when administered to adults 65 years of age and older?
   Voting results: ten committee members voted "yes", one voted "no", and one abstained.

It was discussed that while Fluad did not successfully meet its co-primary endpoint for superior immune responses compared to Agriflu in the phase 3 safety and immunogenicity study V70_27, it did meet success criteria for the co-primary endpoint of immunologic non-inferiority compared with the US licensed product Agriflu. The safety of the product was discussed regarding the increased rates or local and systemic reactogenicity compared to Agriflu in the Phase 3 trial V70_27. It was noted that most of this increase was in mild or moderate reactogenicity and that the risk of this product was offset by the benefit of preventing influenza illness and its associated complications in the elderly. The committee explored the need to evaluate the safety of Fluad after annual revaccination. The data from pooled revaccination studies conducted outside the United Stated and not under IND were discussed (See section 8.2 for review of these data)and some committee members suggested that considerations be given to conducting studies to evaluate the safety of the product following revaccination

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study V70_27 NCT01162122: Primary Study for Safety and Immunogenicity of Fluad

Study V70_27 was entitled, "A Phase III, Randomized, Controlled, Observer-Blind, Multicenter Study to Evaluate the Safety and Immunogenicity and the Consistency of Three Consecutive Lots of an MF59C.1 Adjuvanted Trivalent Subunit Influenza Vaccine in Elderly Subjects Aged 65 Years and Older".

The study began enrollment on August 13, 2010 and the final Day 366 clinic visit with the last subject occurred on November 16th, 2011. An interim analysis was planned at 6-months after the last subject's first visit and occurred on August 3, 2011, with group-unblinding but not individual unblinding of subjects. The database was locked and all data were unblinded on November 29, 2011.

6.1.1 Objectives

The co-primary immunogenicity objectives were to evaluate lot consistency of Fluad and then immunologic noninferiority and superiority of Fluad compared to Agriflu. Day 22 GMT ratios and seroconversion rate differences comparing Fluad to Agriflu were considered the surrogate marker that is reasonably likely to predict clinical benefit for consideration of licensure under the accelerated approval pathway. The requirement for demonstration of safety under the accelerated approval regulations is the same as for "traditional" approval and this was characterized using descriptive statistics to compare Fluad against Agriflu for 1 year postvaccination.

Selected Co-primary Immunogenicity Objectives

1. To demonstrate immunologic equivalence of 3 consecutive production lots of Fluad as measured by HAI GMTs at Day 22 for each virus strain (lot-to-lot consistency).

2. To demonstrate immunologic noninferiority of Fluad compared to Agriflu with regards to all 3 vaccine strains as measured by GMT ratios and seroconversion rate differences at Day 22.

3. To demonstrate immunologic superiority of Fluad compared to Agriflu with regards to at least 2 of 3 of the vaccine strains as measured by GMT ratios and seroconversion rate differences at Day 22.

Reviewer comment: These objectives were defined per the statistical analysis plan. A fourth co-primary endpoint to evaluate immunogenicity of Fluad according to CHMP (the EMA's Committee for Medicinal Products for Human Use) criteria was added by the Applicant after the interim analysis was conducted on partially unblinded data and was descriptive only in nature. This endpoint will not be discussed further as it does not impact the clinical assessment of Fluad or provide data that pertain to the proposed indication.

Selected Secondary Immunogenicity and Effectiveness Objectives

1. To demonstrate immunologic noninferiority for all 3 vaccine strains of Fluad compared to Agriflu and then to evaluate for immunologic superiority with regards to at least 2 of

the 3 vaccine strains in high-risk subjects as measured by GMT ratios and seroconversion rate differences at Day 22. High-risk subjects had 1 or more of the following predefined comorbidities: congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic diseases, renal insufficiency (4% to 5%), and the most commonly reported neurological/neuromuscular or metabolic conditions including diabetes mellitus.

2. To demonstrate immunologic noninferiority of Fluad compared to Agriflu for three heterologous strains selected by the Applicant and to demonstrate immunologic superiority of Fluad compared to Agriflu for 2 of the 3 heterologous strains in all subjects and as measured by GMT ratios and seroconversion rate differences at Day 22.

3. To compare durability of immune response of Fluad compared to Agriflu for vaccine strains as measured by GMT ratios at 6 months and 1 year postvaccination

4. To evaluate the clinical effectiveness of Fluad compared to Agriflu

Reviewer comment: Three other secondary endpoints defined by the Applicant will not be further discussed in this review as they will not impact the clinical assessment of this product and do not provide data that pertains to the proposed indication. The review will not discuss immunogenicity in high-risk subjects against heterologous strains because it will be discussed for all subjects and the endpoints success criteria of superiority were not met for all subjects or for high-risk subjects. The review will not discuss antibody persistence as defined by seroconversion rate differences since at this time point a difference between the two groups may not be clinically meaningful if the antibody levels have declined in both groups. Antibody persistence against three heterologous strains will not be discussed since these strains were selected by the Applicant without CBER input; endpoint criteria were not predefined; and the sample size was not powered to demonstrate a statistical difference. Of note, despite these limitations, antibody persistence with regard to the vaccine strains will be briefly discussed since it is pertinent to one of the plausible benefits of the adjuvant (i.e., the improve the duration of protection). Evaluation of Agriflu immunogenicity based on CHMP criteria will not be discussed because this endpoint is descriptive in nature and does not impact the clinical assessment of Fluad and or provide data that pertain to the proposed indication.

<u>Safety Objectives</u>

1. To describe safety and tolerability of Fluad compared to Agriflu in all subjects through Day 8 following vaccination and all adverse events AEs and SAEs through Day 22.

2. To describe SAEs, new onset chronic diseases, and AEs resulting in withdrawal from the study through 1 year post vaccination.

6.1.2 Design Overview

This was a phase 3, randomized, controlled, observer-blind, multicenter study in subjects 65 years of age and older. Subjects were grouped into 2 age cohorts: 65 to 75 years and >75 years, and were randomly allocated in a 1:1:1:3 ratio to receive 1 of 3 lots of Fluad or Agriflu.

Blood samples for immunogenicity testing were collected prevaccination on Day 1 and postvaccination on Day 22 to evaluate the primary and secondary immunogenicity endpoints. It was planned that at selected sites in the United States the first 700 subjects who were enrolled would have additional blood collected at 6 months and 1 year postvaccination. Of these subjects, 400 had samples tested for durability of immune response while the remaining 300 were stored for future research. Two hundred subjects among those selected for antibody persistence testing were to undergo laboratory safety assessment of blood chemistry and hematology prevaccination on Day 1 and again on Day 8.

Subjects were followed for solicited AEs by diary card through Day 8 post vaccination. Unsolicited EAs were collected at the Day 22 clinical visit. SAEs, deaths, AEs leading to study withdrawal and new onset chronic disease were monitored for one year following vaccination.

Reviewer comment: Although it was stated in the protocol that new onset chronic disease would be collected for the entire study duration (1 year) the definition of this entity was not provided in the protocol or clinical study report. This review will also discuss AESIs which were not prespecified but were captured post hoc using MedDRA (Medical Dictionary for Regulatory Activities) *system organ class and preferred terms were used to search the database. AESIs comprised a list of 204 medical diagnoses that may have immunologic or inflammatory (including neuroinflammatory) origins, or other conditions such as narcolepsy, that either pose a theoretical concern or have been previously identified in association with use of novel adjuvants (see section 6.1.12.5 for the database search terms queried by the Applicant). It is important to recognize that this focused approach is exploratory in nature and in all cases a causal link has not been established.*

6.1.3 Population

Inclusion Criteria

- Aged ≥ 65 years on the Day of vaccination
- Written informed consent obtained
- Able to attend scheduled visits, receive phone calls, and adhere to study procedures

Exclusion Criteria

- Behavioral, psychiatric, or cognitive condition that would interfere with the subjects ability to comprehend and/or follow study procedures
- Medical illness that might pose additional risk to the subject due to study participation
- Immune impairment or manipulation including
    - Receipt of chemotherapy within past 12 months or systemic corticosteroids within 90 Days of study participation
    - Receipt of any blood products within 90 Days of study or study participation
    - HIV infection, congenital immunodeficiency or known thymic or splenic dysfunction
- Known bleeding diathesis or condition associated with prolonged bleeding
- History of Guillain-Barré syndrome
- Receipt of another investigational product within 30 Days of study participation

- Receipt of another inactivated vaccine within 2 weeks prior to study vaccination; or receipt of a live-attenuated vaccine 4 weeks prior to vaccination; or plan to receive any vaccine within 3 weeks after study vaccination
- Receipt of vaccination against seasonal influenza within last 6 months
- Research staff directly involved with the clinical study or their family/household members
- Oral temperature ≥ 38°C on Day or study vaccination; participation may be postponed until subject afebrile for ≥ 3 Days and acute clinical condition stabilized.
- History of substance abuse within past 2 years
- Elective surgery planned to occur during first 3 weeks of vaccine administration or anytime during the study such that it might pose additional risk to subject
- Subjects deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized without his/her consent
- Subjects from whom blood cannot be drawn at visit Day 1

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomly assigned to receive one of three lots of Fluad or Agriflu in a 1:1:1:3 ratio, respectively. Product information and lot numbers are provided in Table 4 below.

Table 4. Vaccines used in study V70_27

Vaccine	**Composition (0.5 mL)**
Investigational product:	Fluad®: Influenza Virus Vaccine, Adjuvanted (Trivalent, Types A and B)
Active ingredients:	A/California/7/2009 (H1N1)-like strain (≥ 15 µg HA[1]) A/Perth/16/2009 (H3N2)-like strain (≥ 15 µg HA) B/Brisbane/60/2008-like strain (≥ 15 µg HA)
Adjuvant:	Squalene (9.75 mg) Polysorbate 80 (1.175 mg) Sorbitan trioleate (1.175 mg) Sodium citrate monohydrate (0.66 mg) Citric acid (0.04 mg)
Excipients:	(b) (4)
Lot numbers:	A52P14H1, A52P15H1, A52P16H1
Investigational product:	Agriflu®:
Active ingredients:	A/California/7/2009 (H1N1)-like strain (≥ 15 µg HA) A/Perth/16/2009 (H3N2)-like strain (≥ 15 µg HA) B/Brisbane/60/2008-like strain (≥ 15 µg HA)

Vaccine	Composition (0.5 mL)
Adjuvant:	None
Excipients:	(b) (4)
Lot number:	107001A

Source: Adapted from BLA 125510/0.11; Clinical Study Report V70_27 Tables 9.4.2-1 and 9.4.2-2
[1]HA: Hemagglutinin Antigen

Reviewer comment: All vaccines were administered at the beginning of the 2010/2011 influenza season and contained the antigen composition that was recommended by the WHO and VRBPAC for the 2010/2011 Northern Hemisphere influenza season.

6.1.5 Directions for Use

Subjects received a single 0.5 mL dose of the assigned study vaccine by IM injection to the deltoid muscle of their nondominant arm by the qualified health care personnel. This individual was unblinded but would have no further contact with the subject and was instructed not to reveal the identity of the vaccine to the study participants or site investigators.

6.1.6 Sites and Centers

The trial involved a total of 38 sites including 21 sites in the United States (30% of subjects); 11 sites in the Philippines (53% of subjects), 4 sites in Columbia (14% of subjects), and 2 sites in Panama (3% of subjects).

6.1.7 Surveillance/Monitoring

Monitoring procedures for study V70_27 are described in Table 5.

Table 5. Monitoring and surveillance procedures for study V70_27

Study Day	Day 1	Day 8	Day 22[1]	Days 91, 181, 271	Day 366
Procedures performed	-ICF -Medical history -Concomitant medications -Physical Examination -Serology blood draw -Safety labs[2] -Eligibility -Randomization -Study vaccine -Dispense diary cards #1 and #2	-Confirm subject has filled out diary card #1 -Assess for any SAEs -Limited physical assessment[3] -Safety labs[2]	-Limited physical assessment -Check and collect diary cards #1 and #2 -Assess local & Systemic reactions And AEs/SAEs -Concomitant medications -Blood draw for immunogenicity -Dispense memory aid	-Review memory aid -AEs leading to withdrawal/SAEs/ NOCD[4] -Concomitant medications -Exacerbation of pre-existing chronic disease -Mortality -Healthcare Utilization -Day 181 blood draw in antibody persistence group	-Limited physical Assessment (in a subset of subjects) -Review memory aid -AEs leading to withdrawal/SAEs/ NOCD[4] -Exacerbation of pre-existing chronic disease -Mortality -Healthcare utilization -Termination -Blood draw in antibody persistence group

Source: Adapted from BLA 125510/0.11; Clinical Study Report V70_27 Section 9.1, figure 9.1-1 Study Procedures flowchart

[1]Influenza-Like Illness surveillance period with 2-week and 4-week telephone contact through 1 year postvaccination

[2]Blood drawn for safety subset in antibody persistence group

[3]For antibody persistence group

[4]NOCD: new-onset chronic disease

6.1.8 Endpoints and Criteria for Study Success

Study endpoints are described below. For definitions of the per protocol set (PPS) and the full analysis set (FAS) populations utilized for these analyses see Section 6.1.10.1. For evaluation of seroconversion rate differences, seroconversion was defined as HAI ≥1:40 for subjects who were seronegative at baseline (HAI titer < 1:10), or a 4-fold increase in HAI titer for subjects who were seropositive at baseline (HAI ≥ 1:10).

Lot equivalency between 3 sequential lots of Fluad was evaluated first, and if demonstrated, the three lots were pooled and compared to Agriflu for immunologic noninferiority. If success criteria for immunologic noninferiority were met, then immunologic superiority by both GMT ratios (Fluad/Agriflu) and seroconversion rate differences (Fluad – Agriflu) were evaluated. The success criteria for each endpoint and the population that was analyzed, as pre-specified in the statistical analysis, plan is listed below.

Co-Primary Endpoints

1. Lot equivalence (Per Protocol Set [PPS, defined in Section 6.1.10.1]) for each of the three vaccine strains (A/H1N1, A/H3N2, and B) between each pair of lots (i.e. Group A and B, Group B and C, Group A and C) was demonstrated for GMTs if the two-sided 95% CI of the ratios of Day 22 GMTs between each pair of Fluad vaccine lots fell within the range of 0.67 to 1.50.

2. Non-inferiority (PPS) was demonstrated if the lower bound (LB) of the 95% CI for Day 22 postvaccination GMT ratios (Fluad / Agriflu) were greater than 0.67, and if the LB the 95% CI for Day 22 postvaccination seroconversion rate differences (Fluad - Agriflu) were greater than -10% for all 3 vaccine strains.

3. Superiority (FAS) was demonstrated if the LB of the 95% CI for Day 22 postvaccination GMT ratios (Fluad / Agriflu) were greater than 1.5 and if the LB of the 95% CI for Day 22 postvaccination seroconversion rate differences (Fluad - Agriflu) were greater than 10% for at least 2 of the 3 vaccine strains.

Selected Secondary Endpoints

Analyses for the below endpoints 1 and 2 were evaluated using the same criteria as described for the primary endpoints (noninferiority, and if met, then then superiority based on GMT ratios [Fluad / Agriflu] and seroconversion rate differences [Fluad – Agriflu].)

1. Superiority of Fluad compared to Agriflu for vaccine strains in high-risk subjects (PPS).

2. Superiority of Fluad vs. Agriflu for three heterologous strains selected by the applicant in all subjects and in high-risk subjects (FAS).

3. Antibody persistence was evaluated in a subset of subjects by comparing GMT ratios (Fluad/ Agriflu) at 6 months and 1 year postvaccination.

4. Clinical Effectiveness of Fluad vs Agriflu: To evaluate the clinical effectiveness of Fluad compared to Agriflu the rates of clinical ILI (e.g., not necessarily microbiologically confirmed), exacerbation of pre-existing chronic disease, the incidence of health care utilization (defined as emergency room visits, unscheduled physician visits, and hospitalizations due to influenza, pneumonia, cardiac, cardiopulmonary, or pulmonary disease), and mortality will be compared. Relative vaccine efficacy (VE) was calculated as 1 – RR, where RR is the relative risk of effectiveness endpoint in the FLUAD group compared to the Agriflu group.

Safety Endpoints:

- Local and systemic reactions occurring within 1 week after administration
- Unsolicited AEs evaluated through study Day 22
- All AEs leading to study withdrawal, SAEs, and deaths reported for 1 year postvaccination
- Any new onset chronic disease reported in a subject for 1 year postvaccination
- Changes in serum chemistry and hematology as assessed by clinical laboratory tests in a subset of subjects enrolled in the US who were also participating the antibody persistence analysis subset.

Reviewer comment: New onset chronic disease and SAEs were used to evaluate for AESIs.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Primary hypotheses addressed the endpoints are described above in Section 6.1.8.

The total target sample size of the study was approximately 7000; 3500 to receive Fluad (1167 per lot) and 3500 to receive Agriflu). The expected drop-out rate was 10% and the remaining anticipated evaluable sample size of 3150 per group. Sample size for immunogenicity endpoints was estimated to show lot equivalency with 99.1%; noninferiority with 99.4% power; and superiority with 96% power; with an overall power of 94.6%. Each of the calculations assumed a type I of 0.025.

Please see the statistical review for detailed description of the statistical analysis.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Below are the definitions of each population to be analyzed. To be included in any population the subject must have signed the informed consent form.

All Enrolled Population
All subjects who completed screening procedures, and provided demographic data.

All Randomized Subjects
All randomized subjects.

Full Analysis Set (FAS), Immunogenicity Day 22
All randomized subjects who received a trial vaccination and provided evaluable serum samples both at Day 1 (baseline) and at Day 22. In the event that the administered vaccine was not assigned according to randomization, subjects were to be analyzed as randomized in the FAS. In the event that subjects were randomized in the wrong age cohort, subjects were to be analyzed in the age cohort they were randomized to in the trial.

Per Protocol Set (PPS), Immunogenicity Day 22
All subjects in the FAS who received the correct vaccine, provided evaluable serum samples on both Day 1 and Day 22, and had no major protocol deviation prior to unblinding. A major deviation was defined as a deviation from per protocol procedures likely to significantly impact the Day 22 immunogenicity results for that subject. Protocol deviations were to be identified prior to unblinding and analysis of the data. Major deviations include:

- Subjects outside age cutoff (i.e., < 65 years)
- Subject enrolled who did not meet trial entry criteria
- Subjects who did not attend the scheduled visits for blood draws:
    - Day 1 (prior to vaccination)
    - Inside of the Day 22 visit window (Days 22 through 25)
- Subjects who did not receive the correct trial vaccine
- Subjects randomized in the wrong age cohort
- Subjects who did not attend visits within the allowed window (see above)

- Subjects who prematurely withdrew from the trial (e.g., lost to follow up or withdrew consent)
- Subjects who developed withdrawal criteria during the trial, but were not withdrawn
- Subjects missing antibody data due to technical problems
- Subjects who received a concomitant medication not permitted by the protocol (in the judgment of the cluster physician)
- Deviations identified through monitoring listings might be considered as well

FAS, Antibody Persistence Testing
All subjects in the randomized population at US sites who (i) received a study vaccination and (ii) provided evaluable blood samples at Day 1, Day 22, Day 181, and Day 366. In the event that the administered vaccine was not assigned according to randomization, subjects were to be analyzed as randomized in the FAS. In the event the subject received nonstudy influenza vaccine prior to Day 366, the subject was to be removed from the analysis.

FAS, Effectiveness: All subjects in the randomized population who received a study vaccination. In the event that the administered vaccine was not assigned according to randomization, subjects were to be analyzed as randomized in the FAS.

Modified Full Analysis Set (mFAS), Effectiveness: All subjects included in the Effectiveness FAS, but for those subjects who received a nonstudy influenza vaccination during the follow-up phase, any ILI/health care utilization/exacerbation of preexisting chronic diseases/deaths occurring after the nonstudy vaccination were not included in the analysis. In the event that the administered vaccine was not assigned according to randomization, subjects were to be analyzed as randomized in the FAS.

Safety Set: All randomized subjects who received a study vaccination and provided post-vaccination safety data.

6.1.10.1.1 Demographics
Review of demographic data on those enrolled, as outlined in Table 6, revealed a well-balanced distribution between study arms with overall percentages of 36% male, 53% Asian, 28% Caucasian, 18% Hispanic, 1% Black and < 1% each Other, Native American, Alaskan, Pacific Islander, and Hawaiian. Because 70% of subjects were enrolled outside of the United States, the demographic distribution of subjects in this study is heavily influenced by that of those countries and is less reflective of the demographics solely within the United States.

Table 6. Demographic Characteristics of Subjects in the FAS[1] Population for Study V70_27

Parameter	Fluad N[2] = 3479	Agriflu N = 3482	Total N=6961
Age (Mean ± SD; years)	71.9±5.3	71.8±5.3	71.9±5.3
Gender:			
Male	1252 (36%)	1178 (34%)	2430 (35%)
Female	2227 (64%)	2304 (66%)	4531 (65%)
Age Cohorts :			
65-75 years	2504 (72%)	2531 (73%)	5035 (72%)

Parameter	Fluad N[2] = 3479	Agriflu N = 3482	Total N=6961
>75 years	975 (28%)	951 (27%)	1926 (28%)
Country:			
Colombia	503 (14%)	495 (14%)	998 (14%)
Panama	108 (3%)	102 (3%)	210 (3%)
Philippines	1832 (53%)	1830 (53%)	3662 (53%)
United States	1036 (30%)	1055 (30%)	2091 (30%)
Ethnic Origin:			
Asian	1837 (53%)	1840 (53%)	3677 (53%)
Black	44 (1%)	39 (1%)	83 (1%)
Caucasian	969 (28%)	971 (28%)	1940 (28%)
Hispanic	616 (18%)	613 (18%)	1229 (18%)
Other	11 (<1%)	16 (<1%)	27 (<1%)
Native American/Alaskan	1 (<1%)	3 (<1%)	4 (<1%)
Pacific Islander /Hawaiian	1 (<1%)	0	1 (<1%)

Adapted from 125510/0.11: Clinical Study Report Table 11.2-1
[1]FAS: full analysis set
[2]N: number of subjects

Reviewer comment: A reason as to why more women than men were enrolled onto study V70_27 was not provided by the Applicant. However, possible explanations include differences in longevity, health status and/or health-care utilization such that fewer men were recruited. However, because seroconversion rate differences and GMT ratios when comparing Fluad to Agriflu were similar between men and women, this imbalance should not impact the conclusions drawn from this study.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Thirty-six percent of subjects were considered high-risk for influenza infection and its complications. This high-risk population included any subject with one or more of the following predefined comorbidities: congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic diseases, renal insufficiency (4% to 5%), and the most commonly reported neurological/neuromuscular or metabolic conditions including diabetes mellitus.

6.1.10.1.3 Subject Disposition
Table 7 outlines subject disposition. A full definition of each population is contained above in Section 6.1.10.1.

Table 7. Subject Disposition for Study V70_27

Disposition	Fluad	Agriflu	Total
Enrolled	n/a	n/a	7109
Randomized	3552	3552	7104
Vaccinated[1,2]	3541 (100%)	3541 (100%)	7082 (100%)
FAS[3]	3479 (99%)	3482 (98%)	6961 (94%)
PPS[4]	3227 (91%)	3259 (92%)	6486 (92%)
Antibody persistence group	189 (5%)	191 (5%)	380 (5%)

Disposition	Fluad	Agriflu	Total
FAS, Effectiveness	3498 (99%)	3502 (99%)	7000 (99%)
Modified FAS	3497 (99%)	3499 (99%)	6996 (99%)
Safety Set[1]	3545 (>99%)	3537 (>99%)	7082(100%)
Premature withdrawals (total)	191 (5%)	196 (6%)	392 (6%)
missing reason	1 (<1%)	0	1 (<1%)
death[5]	51 (1%)	46 (1%)	97 (1%)
AE	3 (<1%)	2 (<1%)	5 (<1%)
withdrew consent	52 (1%)	43 (<1%)	95 (1%)
lost to follow-up	73 (2%)	91 (3%)	164 (2%)
inappropriate enrollment	5 (<1%)	4 (<1%)	9 (<1%)
administrative reason	1 (<1%)	1 (<1%)	2 (<1%)
protocol deviation	2 (<1%)	2 (<1%)	4 (<1%)
unable to classify	3 (<1%)	7 (<1%)	10 (<1%)

Source: Adapted from BLA 125510/0.11 Clinical Study Report Table 10.1-1 and figures 10.1-1, 10.1-2 and 10.1-4.

[1]Seven subjects randomized to Agriflu received Fluad and 3 subjects randomized to Fluad received Agriflu. Safety analysis evaluated based on vaccine received, not randomization group.

[2]Total number of subjects who received any vaccine (whether or not it was correct) are defined as 100%

[3]FAS: full analysis set

[4]PPS: per-protocol set

[5]One subject withdrew after developing an AE (lung neoplasm) that subsequently led to death; the death is not included in this table because the AE, rather than death, was the cause of the withdrawal.

Reviewer comment: The sample size calculations assumed that 7000 subjects were enrolled and that at least 90% completed the study. Primary endpoints evaluated the FAS and the PPS for which the completion rate was 94% and 92%, respectively, as shown in above in Table 7.

6.1.11 Efficacy Analyses

Blood samples for immunogenicity were obtained on Day 1 immediately before vaccination and then at Day 22. The statistical analysis plan as proposed by the sponsor with concurrence from CBER specified that noninferiority would be evaluated in the PPS and superiority in the FAS. Of note, due to a high completion rate in both groups, additional analysis for superiority conducted on the PPS resulted in the same conclusions with regards to superiority (see Section 6.1.10.1 for a definition of the analysis populations). Selected secondary endpoints as described in Objectives, Section 6.1.1 and Endpoints, Section 6.1.8 are described below in section 6.1.11.2.

6.1.11.1 Analyses of Primary Endpoints

Co-primary Objective 1: Lot Equivalency of Fluad

The first co-primary immunogenicity objective was to evaluate immunologic equivalence of three consecutive production lots of Fluad as measured by HAI GMTs at Day 22 for each virus strain. The 95% CIs of the Day 22 GMT ratios for the pairwise lot comparisons all fell within the

equivalence range of 0.67 to 1.5. Therefore, having confirmed immunologic equivalence of the lots, data from the three lots were pooled into a single Fluad group for comparison with the Agriflu group (Table 8).

Table 8. Geometric Mean Hemagglutinin Inhibition Antibody Titers and Lot-To-Lot Ratios at Day 1 and Day 22 for Each Lot of Fluad for Study V70_27 (PPS[1])

Strain	Study Day	Lot 1 GMT[2] (95% CI[3]) N[4] = 1072	Lot 2 GMT (95% CI) N = 1078	Lot 3 GMT (95% CI) N = 1075	Lot 1: Lot2[5]	Lot 1: Lot 3	Lot 2: Lot 3
A California H1N1/2009-like	Day 1	7.19 (6.55, 7.89)	7.84 (7.15, 8.6)	8.04 (7.33, 8.82)	0.92 (0.83, 1.01)	0.89 (0.81, 0.99)	0.98 (0.88, 1.08)
A California H1N1/2009-like	Day 22[6]	105 (95, 116)	94 (85, 103)	99 (90, 110)	1.12 (1.03, 1.24)	1.06 (0.95, 1.17)	0.95 (0.85, 1.05)
A H3N2 Perth/2009-like	Day 1	24 (22-28)	26 (23, 30)	25 (22, 28)	0.93 (0.82, 1.06)	0.97 (0.85, 1.11)	1.05 (0.92, 1.2)
A H3N2 Perth/2009-like	Day 22	274 (251, 299)	271 (249, 296)	278 (255, 303)	1.01 (0.92, 1.11)	0.99 (0.91, 1.08)	0.98 (0.89, 1.07)
Influenza B Brisbane/2008-like	Day 1	6.04 (5.62, 6.49)	6.22 (5.79, 6.68)	6.26 (5.83, 6.72)	0.97 (0.90, 1.05)	0.97 (0.89, 1.04)	0.99 (0.92, 1.07)
Influenza B Brisbane/2008-like	Day 22	28 (26, 31)	28 (26, 31)	29 (27, 32)	1.00 (0.91, 1.1)	0.96 (0.87, 1.05)	0.96 (0.87, 1.05)

Adapted from 125510/0.11: Clinical Study Report Table 11.4.1.1-1

[1]PPS: per protocol set

[2]GMT: geometric mean titers

[3]CI: confidence interval

[4]N: number of subjects

[5]Pre-specified lot equivalency criteria met if 95%CI for lot ratios fell within 0.67 to 1.5

[6]Day 22 GMTs and vaccine group GMT ratios are adjusted for baseline titer, country, and age cohort

Co-Primary Objective 2: Immunologic Noninferiority of Fluad Compared to Agriflu at Day 22

Non-inferiority of Fluad compared to Agriflu, (per criteria outlined in Section 6.1.8), was demonstrated for GMTs and seroconversion rates to all three vaccine strains (Tables 9 and 10).

Table 9. Non-Inferiority[1] Comparison of Post-Vaccination Geometric Mean Day 1 and Day 22 Hemagglutinin Inhibition Antibody Titers Against Influenza Vaccine Strains for Study V70_27 (PPS[2])

Strain	Study Day	Fluad GMT[3] (95% CI[4]) N[5] = 3225	Agriflu GMT (95% CI) N = 3256	Ratio[6] Fluad: Agriflu (95% CI)
A California H1N1/2009-like	Day 1	7.64 (7.2, 8.11)	7.68 (7.23, 8.14)	1.00 (0.94, 1.05)
A California H1N1/2009-like	Day 22	99 (93, 106)	70 (66, 75)	1.4 (1.32, 1.49)
A H3N2 Perth/2009-like	Day 1	27 (25, 29)	26 (24, 28)	1.02 (0.84, 1.10)
A H3N2 Perth/2009-like	Day 22	272 (257-288)	169 (159, 179)	1.61 (1.52, 1.7)
Influenza B Brisbane/2008-like	Day 1	6.15 (5.88, 6.43)	6.12 (5.85-6.4)	1.00(0.96, 1.05)
Influenza B Brisbane/2008-like	Day 22	28 (26-29)	24 (23-26)	1.15 (1.08, 1.21)

Adapted from 125510/0.11: Clinical Study Report Table 11.4.1.1-2

[1]Non-inferiority (GMTs): lower bound of 95%CI for ratio of Fluad: Agriflu > 0.67

[2]PPS: per protocol set

[3]GMT: geometric mean titers

[4]CI: confidence interval

[5]N: number of subjects

[6]Day 22 Ratio is adjusted for baseline titer, country, and age cohort

Table 10. Non-Inferiority[1] Comparison of Seroconversion[2] in Hemagglutinin Inhibition Antibody Titers Against Influenza Vaccine Strains at Day 22 for Trial V70_27 (PPS[3])

Strain	Fluad % (95% CI[4]) N[5] = 3225	Agriflu % (95% CI) N = 3256	Difference[6]: Fluad-Agriflu (95%CI)
A H1N1 California/2009-like	69 (67, 70)	58 (57, 60)	9.8 (7.5, 12.1)
A H3N2 Perth/2009-like	73 (71, 74)	58 (56, 60)	13.9 (11.7-16.1)
Influenza B Brisbane/2008-like	33 (31, 35)	29 (28, 31)	3.2 (1.1, 5.3)

Adapted from 125510/0.11: Clinical Study Report Table 11.2.1.1-3

[1]Non-inferiority (% seroconversion): lower bound of 95% CI for difference of Fluad-Agriflu >-10%

[2]Seroconversion defined as a prevaccination HI titer <10 and postvaccination HI titer ≥ 40, or at least a 4-fold increase in HI titer from prevaccination titer ≥ 10

[3]PPS: per protocol set

[4]CI: confidence interval

[5]N: number of subjects

[6]Day 22 differences are adjusted for baseline titer, country and age cohort

Co-Primary Objective 3: Immunologic Superiority of Fluad Compared to Agriflu at Day 22

The criteria for immunologic superiority of GMT and seroconversion rate differences were met for one of three homologous strains, H3N2 (Tables 11 and 12).

Table 11. Superiority[1] Comparison of Post-Vaccination Geometric Mean Day 1 and Day 22 Hemagglutinin Inhibition Antibody Titers Against Influenza Vaccine Strains for Study V70_27 (FAS[2])

Strain	Study Day	Fluad GMT[3] (95% CI[4]) N[5] = 3477	Agriflu GMT (95% CI) N=3479	Ratio[6] Fluad: Agriflu (95% CI)
A H1N1 California /2009-like	Day 1	8 (7, 8)	8 (7, 8)	1.01 (0.95, 1.06)
A H1N1 California /2009-like	Day 22	98 (92, 104)	71 (67, 76)	1.37 (1.29, 1.46)
A H3N2 Perth/2009-like	Day 1	27 (25, 29)	26 (24, 28)	1.03 (0.95, 1.11)
A H3N2 Perth/2009-like	Day 22	267 (253, 282)	167 (158, 176)	1.6 (1.51, 1.68)
Influenza B Brisbane/2008-like	Day 1	6 (6, 6)	6 (6, 6,)	1.01 (0.97, 1.05)
Influenza B Brisbane/2008-like	Day 22	27 (26, 29)	24 (23, 25)	1.14 (1.08, 1.20)

Adapted from 125510/0.11: Clinical Study Report Table 11.4.1.1-4

[1]Superiority (GMTs): lower bound of 95%CI for ratio of Fluad: Agriflu > 1.5

[2]FAS: full analysis set

[3]GMT: geometric mean titers

[4]CI: confidence interval

[5]N: number of subjects

[6]Day 22 ratio is adjusted for baseline titer, country and age cohort

Table 12. Superiority[1] Comparison of Seroconversion[2] in Hemagglutinin Inhibition Antibody Titers Against Influenza Vaccine Strains at Day 22 for Trial V70_27 (FAS[3])

Strain	Fluad % (95% CI[4]) N[5]=3477	Agriflu % (95% CI) N=3479	Difference[6]: Fluad-Agriflu (95%CI)
A H1N1 California /2009-like	68 (67, 70)	59 (57, 60)	9.6 (7.4, 11.8)
A H3N2 Perth/2009-like	72 (71, 74)	58 (56, 60)	13.8 (11.7, 16)
Influenza B Brisbane/2008-like	33 (31, 34)	30 (28, 31)	3 (1, 5)

Adapted from 125510/0.11: Clinical Study Report 11.4.1.1-5

[1]Superiority (% seroconversion): lower bound of 95% CI for difference of Fluad-Agriflu >10%

[2]Seroconversion defined as a prevaccination HI titer <10 and postvaccination HI titer ≥ 40, or at least a 4-fold increase in HI titer from prevaccination titer ≥ 10

[3]FAS: full analysis set

[4]CI: confidence interval

[5]N: number of subjects

[6]Day 22 differences are adjusted for baseline titer, country and age cohort

Reviewer comment: The study failed to meet the 3rd primary endpoint for immunologic superiority of Fluad compared with Agriflu for 2 of the 3 influenza vaccine strains however, it did meet superiority for the H3N2 Perth/2009-like strain. This may have clinical relevance given the morbidity and mortality associated with H3N2 infection in the elderly, particularly since it is often the predominating seasonal strain, as has been observed in recent years. Further, biological products are licensed under the authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262). Under section 351, BLAs are approved only upon a showing that the product is "safe, pure and potent", for which demonstration of non-inferiority (rather than superiority), compared to a US licensed vaccine, would be sufficient.

6.1.11.2 Analyses of Selected Secondary Endpoints

Superiority of Fluad vs. Agriflu for homologous strains in high risk subjects

The Day 22 postvaccination GMT ratios and seroconversion rate differences between Fluad and Agriflu recipients were analyzed for immunologic noninferiority and then superiority in the subset of subjects (PPS) with pre-defined comorbidities, designated as "high-risk". Although the pre-specified criteria were met for noninferiority (Section 6.1.8), they were not achieved for superiority. High-risk subjects had 1 or more of the following predefined comorbidities: congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic diseases, renal insufficiency (4% to 5%), and the most commonly reported neurological/neuromuscular or metabolic conditions including diabetes mellitus and comprised 37% of the total PPS for each group. (Tables 13 and 14)

Table 13. Superiority[1] Comparison of Post-Vaccination Geometric Mean Day 1 and Day 22 Hemagglutinin Inhibition Antibody Titers Against Influenza Vaccine Strains in High-Risk[2] Subjects for Study V70_27 (PPS[3])

Strain	Study Day	Fluad GMT[4] (95% CI[5]) N[6] = 1194	Agriflu % (95% CI) N = 1190	Ratio[7] Fluad: Agriflu (95% CI)
A H1N1 California /2009-like	Day 1	8.03 (7.3, 8.84)	8.48 (7.7, 9.33)	0.95 (0.86, 1.05)
A H1N1 California /2009-like	Day 22	11 (100, 122)	80 (73, 88)	1.38 (1.25, 1.52)
A H3N2 Perth/2009-like	Day 1	28 (25, 31)	27 (24, 30)	1.04 (0.92, 1.17
A H3N2 Perth/2009-like	Day 22	260 (238, 283)	165 (152, 180)	1.57 (1.44, 1.72)
Influenza B Brisbane/2008-like	Day 1	6.33 (5.89, 6.79)	6.54 (6.09, 7.02)	0.97 (0.9, 1.04)
Influenza B Brisbane/2008-like	Day 22	30 (28, 33)	27 (25, 29)	1.12 (1.03, 1.22)

Adapted from 125510/0.11: Clinical Study Report Table 11.4.1.2-1

[1]Superiority (GMTs): lower bound of 95%CI for ratio of Fluad: Agriflu > 1.5

[2]High-risk subjects had 1 or more of the following predefined comorbidities: congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic diseases, renal insufficiency (4% to 5%), and the most commonly reported neurological/neuromuscular or metabolic conditions including diabetes mellitus.

[3]PPS: per protocol set

[4]GMT: geometric mean titers

[5]CI: confidence interval

[6]N: number of subjects

[7]Day 22 ratio is adjusted for baseline titer, country and age cohort

Table 14. Superiority[1] Comparison of Seroconversion[2] in Hemagglutinin Inhibition Antibody Titers Against Influenza Vaccine Strains at Day 22 in High-Risk[3] Subjects for Trial V70_27 (PPS[4])

Strain	Fluad % (95% CI[5]) N[6] = 3479	Agriflu % (95% CI) N = 3482	Difference[7]: Fluad-Agriflu (95%CI)
A H1N1 California /2009-like	65 (63, 68)	54 (51, 57)	10.9 (7.1, 14.7)
A H3N2 Perth/2009-/like	67 (64, 69)	52 (49, 55)	14 (10.2, 17.7)

Strain	Fluad % (95% CI[5]) N[6] = 3479	Agriflu % (95% CI) N = 3482	Difference[7]: Fluad-Agriflu (95%CI)
Influenza B Brisbane/2008-like	27 (25, 30)	25 (23, 28)	2.2 (-1, 5.4)

Adapted from 125510/0.11: Clinical Study Report Table 11.4.1.2-2

[1]Superiority (% seroconversion): lower bound of 95% CI for difference of Fluad-Agriflu >10%

[2]Seroconversion defined as a prevaccination HI titer <10 and postvaccination HI titer ≥ 40, or at least a 4-fold increase in HI titer from prevaccination titer ≥ 10

[3]High-risk subjects had 1 or more of the following predefined comorbidities: congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic diseases, renal insufficiency (4% to 5%), and the most commonly reported neurological/neuromuscular or metabolic conditions including diabetes mellitus.

[4]PPS: per protocol set

[5]CI: confidence interval

[6]N: number of subjects

[7]Day 22 differences are adjusted for baseline titer, country and age cohort

Superiority of Fluad vs. Agriflu for heterologous strains in high risk subjects

The Day 22 postvaccination GMT ratios and seroconversion rate differences between Fluad and Agriflu recipients were analyzed for immunologic noninferiority and then superiority in the FAS against 3 influenza strains selected by the applicant. Although the pre-specified criteria were met for noninferiority (Section 6.1.8), they were not achieved for superiority. (Tables 15 and 16)

Table 15. Superiority[1] Comparison of Post-Vaccination Geometric Mean Day 1 and Day 22 Hemagglutinin Inhibition Antibody Titers Against 3 Heterologous[2] Influenza Strains for Study V70_27 (FAS[3])

Strain	Study Day	Fluad GMT[4] (95% CI[5]) N[6] = 887	Agriflu % (95% CI) N = 880	Ratio[7] Fluad: Agriflu (95% CI)
A Brisbane H3N2/2007-like	Day 1	33 (29, 38)	33 (29, 38)	1 (0.86, 1.16)
A Brisbane H3N2/2007-like	Day 22	181 (162, 202)	122 (109, 136)	1.49 (1.33, 1.67)
A Wisconsin H3N2/2005-like	Day 1	106 (92, 122)	109 (95, 126)	0.98 (0.84, 1.13)
A Wisconsin H3N2/2005-like	Day 22	508 (643, 557)	369 (336, 405)	1.38 (1.25, 1.52)
Influenza B Malaysia/2506/2004-like	Day 1	9 (8.3, 9.76)	9 (8.3, 9.77)	1 (0.92, 1.09)
Influenza B Malaysia/2506/2004-like	Day 22	44 (40, 48)	40 (36, 44)	1.09 (0.99, 1.21)

Adapted from 125510/0.11: Clinical Study Report Table 11.4.1.2-9

[1]Superiority (GMTs): lower bound of 95%CI for ratio of Fluad: Agriflu > 1.5

[2]Heterologous defined selected by the Applicant and defined as "generally regarded as antigenically distinct from those included in the vaccine"

[3]FAS: full analysis set

[4]GMT: geometric mean titers

[5]CI: confidence interval

[6]N: number of subjects
[7]Day 22 ratio is adjusted for baseline titer, country and age cohort

Table 16. Superiority[1] Comparison of Seroconversion[2] in Hemagglutinin Inhibition Antibody Titers Against 3 Heterologous[3] Strains at Day 22 for Trial V70_27 (FAS[4])

Strain	Fluad GMT[5] (95% CI[6]) N[7] = 887	Agriflu % (95% CI) N = 880	Ratio[8] Fluad: Agriflu (95% CI)
A Brisbane H3N2/2007-like	58 (54, 61)	46 (42, 49)	12.8 (8.4, 17.2)
A Wisconsin H3N2/2005-like	56 (53, 60)	45 (41, 48)	12.5 (8.1, 17)
Influenza B Malaysia/2506/2004-like	41 (38, 44)	38 (35, 41)	4.2 (0, 8.4)

Adapted from 125510/0.11: Clinical Study Report Table 11.4.1.2-10
[1] Superiority (% seroconversion): lower bound of 95% CI for difference of Fluad-Agriflu >10%
[2]Seroconversion defined as a prevaccination HI titer <10 and postvaccination HI titer ≥ 40, or at least
a 4-fold increase in HI titer from prevaccination titer ≥ 10
[3]Heterologous defined selected by the Applicant and defined as "generally regarded as antigenically distinct from those included in the vaccine"
[4]FAS: full analysis set
[5]GMT: geometric mean titers
[6]CI: confidence interval
[7]N: number of subjects
[8]Day 22 ratio is adjusted for baseline titer, country and age cohort

Reviewer comment: The Applicant tested 3 heterologous strains, two of which were H3N2 and one of which was B. CBER input was not obtained, the selection was not pre-specified, and the degree of immunologic divergence from the vaccine strains was not characterized for the purpose of this BLA. Thus, this is a limited evaluation and cannot be extrapolated to predict cross protection more broadly against heterologous strains present in the community. In addition to these caveats, it should be noted that superiority was not demonstrated for any of the 3 strains by the prespecified criteria.

Antibody Persistence

The durability of immune response against the vaccine strains was evaluated in a subset of patients at 6 months and 1 year post vaccination (Table 17). Statistical analyses were descriptive since endpoint criteria were not pre-specified, and the sample size was not powered to demonstrate statistically significant differences.

Table 17. Descriptive Evaluation of Durability of Immune Response Against Influenza Vaccine Strains in the Antibody Persistence Group for Study V70_27

Strain	Study Day	Fluad GMT[1] (95% CI[2]) N[3] = 189	Agriflu % (95% CI) N = 191	Ratio Fluad: Agriflu (95% CI)
A H1N1 California /2009-like	1	17 (14, 20)	19 (16, 23)	0.9 (0.69, 1.18)
A H1N1 California /2009-like	180	35 (30, 42)	34 (29, 40)	1.05 (0.82, 1.33)
A H1N1 California /2009-like	366	25 (21, 30)	26 (22, 31)	0.94 (0.73, 1.22)

Strain	Study Day	Fluad GMT[1] (95% CI[2]) N[3] = 189	Agriflu % (95% CI) N = 191	Ratio Fluad: Agriflu (95% CI)
A H3N2 Perth/2009-like	1	22 (18, 26)	22 (18, 26)	1 (0.77, 1.29
A H3N2 Perth/2009-like	180	62 (52, 73)	46 (39, 54)	1.35 (1.06, 1.71)
A H3N2 Perth/2009-like	366	35 (29, 42)	27 (23, 32)	1.3 (1.01, 1.67)
Influenza B Brisbane/2008-like	1	12 (9.91, 14)	12 (10, 14)	0.97 (0.78, 1.2)
Influenza B Brisbane/2008-like	180	12 (11, 15)	11 (9.51, 13)	1.12 (0.9, 1.39)
Influenza B Brisbane/2008-like	366	10 (8.84, 12)	9.96 (8.58, 12)	1.03 (0.83, 1.27)

Adapted from 125510/0.11: Clinical Study Report Table 11.4.1.2-23

[1]GMT: geometric mean titers

[2]CI: confidence interval

[3]N: number of subjects

Reviewer comment: The 95%CI for A H3N2 Perth/2009-like vaccine strain did not cross 1 at six months or one year postvaccination. However, it did cross 1 for the H1N1 and influenza B vaccine strains and there was an overall decline of the antibody responses relative to baseline titers for all 3 vaccine strains. Given these data, the recommendation for annual revaccination, and the fact that influenza season only lasts approximately 6 months out of the year, these data do not demonstrate statistically important differences between the two vaccines and would not impact the recommendation for annual revaccination, even when there is no seasonal strain change.

Clinical Effectiveness of Fluad vs Agriflu

Effectiveness of the study vaccines was assessed in terms of incidence of subjects with ILI; exacerbation of preexisting chronic disease (defined as unscheduled physician visits, emergency room visits, or hospitalizations for preexisting and chronic congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic disease, renal disease, neurologic/neuromuscular and/or metabolic disease); healthcare utilization (defined as unscheduled physician visits, emergency room visits, or hospitalizations for pneumonia or influenza, cardiopulmonary disease, cardiac disease, or pulmonary disease); and mortality. These data were captured via phone calls occurring every 2-4 weeks (see Section 6.1.12.1 for discussion of study procedures). Analyses were performed using the effectiveness FAS. For the analysis of ILI only, a modified FAS (mFAS) was also defined; the mFAS excluded ILI events that occurred after receipt of any nonstudy influenza vaccine and this analysis did not differ appreciably from evaluation of the FAS effectiveness subset. For description of analysis populations see Table 7, Section 6.1.10. Of note, ILI did not need to be microbiologically confirmed. Overall, there were no important differences in effectiveness noted between vaccine groups overall (Table 18).

Table 18. Clinical Effectiveness of Fluad Compared to Agriflu for Study V70_27.

Effectiveness parameter	Fluad n[1]/N[2] (%)	Agriflu n/N (%)	Risk Ratio of Fluad: Agriflu (95% CI[3])
Influenza-like illness[4]	321/3497 (9%)	314/3499 (9%)	1.02 (0.87, 1.19)
Exacerbation of pre-existing chronic disease	55/1307 (4%)	48/1281 (4%)	1.35 (0.80, 2.26)
Health-care utilization[5]	275/3499 (8%)	289/3502 (8%)	0.95 (0.81, 1.12)
Mortality	52/3450 (1.5%)	46/3541 (1.3%)	1.13 (0.76, 1.68)

Adapted from 125510/0.11: Clinical Study Report Tables 11.4.1.2-13a, 11.4.1.2-13b

[1]n: number of subjects with an event

[2]N: total number of subjects

[3]CI: confidence interval

[4]Influenza-like illness defined as fever (temperature of $\geq$ 37.2 °C) or feverishness (the subjects subjective report of feeling fever or chills) and at least 2 of the following symptoms: headache, myalgia, cough, sore throat from Day 22 through 366.

[5]Defined as unscheduled physician visits, emergency room visits, or hospitalizations for preexisting and chronic congestive heart failure, chronic obstructive pulmonary disease, asthma, hepatic disease, renal disease, neurologic/neuromuscular and/or metabolic disease

[6]Defined as unscheduled physician visits, emergency room visits, of hospitalizations for community acquired pneumonia, cardiopulmonary disease, cardiac disease, or pulmonary disease.

6.1.11.3 Subpopulation Analyses

No immunologic differences were noted with regard to country of origin (i.e., 95% CIs for GMT ratios and seroconversion rate differences for individual countries overlapped with those of the total population, and 95% CIs for GMT ratios and seroconversion rate differences in the United States overlapped with those from the other countries). Subgroup analyses were performed for effectiveness based on country of origin and presence of a high risk chronic medical condition. No important differences were seen based on these evaluations, with all 95% CIs crossing 1 for risk ratios.

Females demonstrated higher GMTs and seroconversion rates than males for both Fluad and Agriflu. The increases were proportional between treatment arms such that the GMT ratios and seroconversion rate differences were relatively comparable (Tables 19 and 20).

Table 19. Day 22 Geometric Mean Titers by Gender and by Vaccine Strain for Fluad and Agriflu for Study V70_27 (FAS[1])

Vaccine strain	Fluad: Males GMT[2] (95% CI[3]) [4]N = 1252	Fluad: Females GMT (95% CI) N = 2225	Agriflu: Males GMT (95% CI) N = 1175	Agriflu: Females GMT (95% CI) N = 2304	Ratio Fluad: Agriflu (95% CI) Males	Ratio Fluad: Agriflu (95% CI) Females
A H1N1 California/2009-like	81 (76, 87)	104 (98, 110)	56 (52, 60)	77 (73, 81)	1.45 (1.31, 1.6)	1.36 (1.26, 1.47)
A H3N2 Perth/2009-like	227 (212, 243)	342 (325, 359)	143 (134, 154)	208 (198, 219)	1.58 (1.44, 1.74)	1.64 (1.53, 1.76)
Influenza B Brisbane/2008-like	25 (24, 27)	24 (23, 25)	21 (20, 22)	22 (21, 22)	1.2 (1.1, 1.32)	1.12 (1.04, 1.2)

[1]FAS: full analysis set
[2]GMT: geometric mean titer
[3]CI: confidence interval
[4]N: total number of subjects

Table 20 Day 22 Seroconversion Rates[1] by Gender and by Vaccine Strain for Fluad and Agriflu for Study V70_27 (FAS[2])

Vaccine strain	Fluad: Males % (95% CI[3]) N[4] = 1252	Fluad: Females % (95% CI) N = 2225	Agriflu: Males % (95% CI) N = 1175	Agriflu: Females % (95% CI) N = 2304	Difference: Fluad-Agriflu (95% CI) Males	Difference: Fluad-Agriflu (95% CI) Females
A H1N1 California/2009-like	64 (61, 67)	71 (69, 73)	51 (48, 53)	63 (61, 65)	13.4 (9.5, 17.3)	8.2 (5.5, 10.9)
A H3N2 Perth/2009-like	67 (64, 70)	75 (73, 77)	52 (49, 55)	61 (59, 63)	15.3 (11.4, 19.1)	13.8 (11.1, 16.5)
Influenza B Brisbane/2008-like	31 (29, 34)	34 (32, 36)	26 (23, 28)	32 (30, 34)	5.7 (2.1, 9.3)	2.1 (-1, 4.9)

[1]Seroconversion defined as a prevaccination HI titer <10 and postvaccination HI titer ≥ 40, or at least a 4-fold increase in HI titer from prevaccination titer ≥ 10
[2]FAS: full analysis set
[3]CI: confidence interval
[4]N: total number of subjects

Reviewer comment: No specific trends were noted in the subgroup analyses that might point to presence of a statistical difference had the study been sufficiently powered. Thus, as demonstrated, it is more likely that there are not meaningful differences between these subgroups. The observation that women demonstrate increased immunogenicity to influenza vaccination (regardless of product) has been previously documented (18).

6.1.11.4 Dropouts and/or Discontinuations

Due to a high completion rate in the context of a relatively large study (see Table 7, Section 6.1.10 for subject disposition), drop-outs and discontinuations had minimal impact on immunogenicity and effectiveness results.

6.1.12 Safety Analyses

6.1.12.1 Methods

7109 subjects were enrolled of whom 7082 (99.6%) were vaccinated and included in the safety analysis (see Table 7 in Section 6.10.1 for complete evaluation of subject disposition). Although 3541 subjects were randomized to each arm, 10 subjects received the wrong study vaccination and were recategorized based on the actual product they received, such that 3545 subjects were included in the Fluad group and 3537 subjects were included in the Agriflu group for the primary safety analyses. The below discussion reflects analyses performed for safety objectives and endpoints outlined in Sections 6.1.1 and 6.1.8, respectively.

Subjects were observed in clinic for 30 minutes postvaccination. They were provided a diary card and were contacted by phone on Day 8 for a query on SAEs; a reminder to complete their first diary card; and prompting to begin recording events on their second diary card through Day 22. They were evaluated in clinic on Day 22 when the diary cards were collected and reviewed. From day 22-366 they were contacted by phone to evaluate (ILI), exacerbation of preexisting chronic disease, health care utilization, and all-cause (except injury), SAEs, and mortality. In the United States, surveillance calls occurred every 2 weeks during the influenza season, (defined in the United States as October 15 through April 30) and every 4 weeks outside the influenza season. For all other countries due to no clear definition of influenza season, surveillance calls occurred every 2 weeks.

6.1.12.2 Overview of Adverse Events

Adverse Events within 30 minutes of vaccination

Thirteen percent of subjects receiving Fluad and 12% of those receiving Agriflu reported an AE within 30 minutes of vaccination, the majority of which were mild in severity (Table 21). The most common local AEs were pain (5% and 4% of subjects for Fluad and Agriflu, respectively) followed by erythema (4% of subjects in both groups) and tenderness (3% in both groups). The most common systemic AE was myalgia (2% and 1% of subjects in Fluad and Agriflu groups, respectively). Grade 3 (severe) AEs in the Fluad group included pain (2 subjects), fever (1 subject), chills (1 subject), myalgia (1 subject), headache (1 subject), and diarrhea (1 subject). Grade 3 AEs in the Agriflu group included arthralgia (1 subject), chills (1 subject), and diarrhea (1 subject). There were no anaphylactic episodes reported.

Table 21. Local and Systemic AEs by Type and Maximum Severity Occurring within 30 Minutes of Vaccination for Study V70_27 (Solicited Safety Set)

Subjects experiencing at least one AE[1] by maximum severity	**Fluad N[2] = 3515 n[3] (%)**	**Agriflu N = 3502 n (%)**
At least one AE (local or systemic)	473 (13%)	435 (12%)
At least one local AE	380 (11%)	435 (10%)
Injection site pain: Total	187 (5%)	140 (4%)
Grade 1 (no interference with activity)	163 (5%)	127 (4%)
Grade 2 (some interference with activity)	22 (1%)	13 (<1%)
Grade 3 (prevents daily activity)	2 (<1%)	0
Injection site tenderness: Total	115 (3%)	93 (3%)

Subjects experiencing at least one AE[1] by maximum severity	**Fluad N[2] = 3515 n[3] (%)**	**Agriflu N = 3502 n (%)**
Grade 1 (no interference with activity)	109 (3%)	87 (2%)
Grade 2 (some interference with activity)	6 (<1%)	6 (<1%)
Grade 3 (prevents daily activity)	0	0
Injection site erythema: Total	143 (4%)	149 (4%)
1mm - <25mm	130 (4%)	139 (4%)
25mm - ≤ 50 mm	13 (< 1%)	10 (<1%)
51mm - ≤100mm	0	0
≥ 100mm	0	0
Injection site induration: Total	38 (1%)	44 (1%)
1mm - <25mm	34 (1%)	44 (1%)
25mm - ≤ 50 mm	4 (<1%)	4 (<1%)
51mm - ≤100mm	0	1 (<1%)
≥ 100mm	0	0
Injection site swelling: Total	16 (<1%)	14 (<1%)
1mm - <25mm	12 (<1%)	12 (<1%)
25mm - ≤ 50 mm	4 (<1%)	2 (<1%)
51mm - ≤100mm	0	0
≥ 100mm	0	0
At least one systemic AE	170 (5%)	144 (4%)
Fever: Total	3 (<1%)	3 (<1%)
Grade 1 (38.0 °C to < 39.0 °C)	2 (<1%)	3 (<1%)
Grade 2 (39.0 °C to < 40.0 °C)	1 (<1%)	0
Grade 3 (≥ 40.0 °C)	1 (<1%)	0
Chills: Total	29 (1%)	22 (1%)
Grade 1 (no interference with activity)	26 (1%)	17 (<1%)
Grade 2 (some interference with activity)	2 (<1%)	4 (<1%)
Grade 3 (prevents daily activity)	1 (<1%)	1 (<1%)
Myalgia: Total	62 (2%)	30 (1%)
Grade 1 (no interference with activity)	56 (2%)	29 (1%)
Grade 2 (some interference with activity)	5 (<1%)	0
Grade 3 (prevents daily activity)	1 (<1%)	1 (<1%)
Arthralgia: Total	30 (1%)	33 (1%)
Grade 1 (no interference with activity)	24 (1%)	24 (1%)
Grade 2 (some interference with activity)	6 (<1%)	8 (<1%)
Grade 3 (prevents daily activity)	0	1 (<1%)
Headache: Total	60 (2%)	59 (2%)
Grade 1 (no interference with activity)	44 (1%)	44 (1%)
Grade 2 (some interference with activity)	15 (<1%)	15 (<1%)
Grade 3 (prevents daily activity)	1 (<1%)	0
Fatigue: Total	47 (1%)	43 (1%)
Grade 1 (no interference with activity)	43 (1%)	30 (1%)
Grade 2 (some interference with activity)	4 (<1%)	13 (<1%)

Subjects experiencing at least one AE[1] by maximum severity	Fluad N[2] = 3515 n[3] (%)	Agriflu N = 3502 n (%)
Grade 3 (prevents daily activity)	0	0
Nausea: Total	9 (<1%)	11 (<1%)
Grade 1 (no interference with activity)	9 (<1%)	6 (<1%)
Grade 2 (some interference with activity)	0	5 (<1%)
Grade 3 (prevents daily activity)	0	0
Vomiting: Total	3 (<1%)	3 (<1%)
Grade 1 (no interference with activity)	3 (<1%)	2 (<1%)
Grade 2 (some interference with activity)	0	1 (<1%)
Grade 3 (prevents daily activity)	0	0
Diarrhea: Total	4 (<1%)	3 (<1%)
Grade 1 (no interference with activity)	3 (<1%)	2 (<1%)
Grade 2 (some interference with activity)	0	0
Grade 3 (prevents daily activity)	1 (<1%)	1 (<1%)

Source: Adapted from BLA 125510/0.11 Clinical Study Report Tables 14.3.1.2.6, 14.3.1.2.16
[1]AE: adverse event
[2]N: total number of subjects
[3]n: number of subjects per group

Local Adverse Reactions within 7 Days of Vaccination

The number of subjects reporting any reactogenicity sign, local or systemic, within 7 days of vaccination was 48% of subjects receiving Fluad and 35% of subjects receiving Agriflu. Local reactions were reported by 35% of Fluad recipients and 20% of Agriflu recipients (Table 22). In both groups the most commonly reported AEs were pain (25% of Fluad recipients and 12% of Agriflu recipients) and tenderness (21% of Fluad recipients and 11% of Agriflu recipients). Although more local AEs were observed in those receiving Fluad, this was due to increased local pain and tenderness of mild severity. Moderate reactogenicity was relatively balanced between groups with no more than 2 percentage points in rate differences). Severe local reactogenicity was balanced between groups and comprised $\leq$ 1% of subjects in each group across all categories; none were deemed potentially life-threatening.

Table 22. Solicited Local AEs by Type and Maximum Severity Occurring within 7 Days of Vaccination for Study V70_27 (Safety Set)

Subjects experiencing at least one local AE[1] by maximum intensity	Fluad N[2] = 3505 n[3] (%)	Agriflu N = 3495 n (%)
At least one AE	1669 (48%)	1239 (35%)
At least one local AE	1214 (35%)	708 (20%)
Pain: Total	875 (25%)	425 (12%)
Grade 1 (no interference with activity)	726 (21%)	351 (10%)
Grade 2 (some interference with activity)	138 (4%)	66 (2%)
Grade 3 (prevents daily activity)	11 (<1%)	8 (<1%)
Tenderness: Total	739 (21%)	391 (11%)
Grade 1 (no interference with activity)	628 (18%)	349 (10%)

Subjects experiencing at least one local AE[1] by maximum intensity	Fluad N[2] = 3505 n[3] (%)	Agriflu N = 3495 n (%)
Grade 2 (some interference with activity)	106 (3%)	36 (1%)
Grade 3 (prevents daily activity)	5 (<1%)	6 (<1%)
Erythema: Total	219 (6%)	179 (5%)
1mm - <25mm	176 (5%)	161 (5%)
25mm - ≤ 50 mm	37 (1%)	17 <1%)
51mm - ≤100mm	6 (<1%)	1 (<1%)
≥ 100mm	0	0
Swelling: Total	89 (3%)	38 (1%)
1mm - <25mm	46 (1%)	23 (1%)
25mm - ≤ 50 mm	35 (1%)	14 (<1%)
51mm - ≤100mm	7 (<1%)	1 <1%)
≥ 100mm	1 (<1%)	0
Induration: Total	127 (4%)	67 (2%)
1mm - <25mm	82 (2%)	50 (1%)
25mm - ≤ 50 mm	35 (1%)	17 (<1%)
51mm - ≤100mm	10 (<1%)	0
≥ 100mm	0	0

Source: Adapted from BLA 125510/0.11 Clinical Study Report Tables 14.3.1.2.7 and 14.3.1.2.17

[1]AE: adverse event

[2]N: total number of subjects

[3]n: number of subjects per group

Systemic Adverse Reactions within 7 Days of Vaccination

Systemic adverse reactions were reported by 32% of Fluad recipients and 26% of Agriflu recipients within 7 days of vaccination (Table 23). In both groups the most commonly reported adverse reactions were myalgia (15% of Fluad recipients and 10% of Agriflu recipients) and fatigue (13% of Fluad recipients and 10% of Agriflu recipients). Slight imbalances in mild and moderate adverse reactions (1 to 2% higher for mild and moderate systemic reactogenicity were reported in the Fluad group aside from myalgia and fatigue noted above) account for higher rates overall of systemic AEs observed in those receiving Fluad. Severe local reactogenicity was balanced between groups and comprised ≤ 1% of subjects in each group across all categories. Potentially life-threatening systemic reactions were defined as those requiring an emergency room visit or hospitalization. In the Fluad group one subject had potentially life-threatening diarrhea and one subject had chills, nausea and vomiting, all potentially life-threatening. Each of three subjects in the Agriflu group had one potentially life-threatening symptom which was headache, fatigue and diarrhea.

Reviewer comment: "Potentially life-threatening" was defined as those events requiring an emergency room visit or hospitalization. Additionally, the percentages of subjects experiencing local reactogenicity are increased in the clinical review compared with the VRBPAC briefing document. For the VRBPAC briefing document, summary tables outlining moderate to severe reactions excluded subjects with 1-25mm reactions were used (defined as type I reactions by the

Applicant). For the BLA, a duplicate set of tables (defined as type II reactions by the Applicant) were utilized which included subjects with local reactions between 1-25mm in diameter.

Table 23. Solicited Systemic AEs by Type and Maximum Severity within 7 Days of Vaccination for Study V70_27 (Safety Set)

Subjects experiencing at least one systemic AE[1] by maximum intensity	Fluad N[2] = 3505 n[3] (%)	Agriflu N = 3495 n (%)
At least one systemic AE	1120 (32%)	902 (26%)
Temperature ≥ 38.0 °C: Total	122 (4%)	116 (3%)
Grade 1 (38.0 °C to < 39.0 °C)	106 (3%)	101 (3%)
Grade 2 (39.0 °C to < 40.0 °C)	13 (<1%)	15 <1%)
Grade 3 (≥ 40.0 °C)	3 (<1%)	0
Grade 4 (potentially life-threatening)[4]	0	0
Chills: Total	235 (7%)	163 (5%)
Grade 1 (no interference with activity)	169 (5%)	111 (3%)
Grade 2 (some interference with activity)	53 (2%)	43 (1%)
Grade 3 (prevents daily activity)	12 (<1%)	9 (<1%)
Grade 4 (potentially life-threatening)	1 (<1%)	0
Myalgia: Total	515 (15%)	339 (10%)
Grade 1 (no interference with activity)	414 (12%)	251 (7%)
Grade 2 (some interference with activity)	91 (3%)	63 (2%)
Grade 3 (prevents daily activity)	10 (<1%)	25 (1%)
Grade 4 (potentially life-threatening)	0	0
Arthralgia: Total	296 (8%)	272 (8%)
Grade 1 (no interference with activity)	232 (7%)	196 (6%)
Grade 2 (some interference with activity)	57 (2%)	56 (2%)
Grade 3 (prevents daily activity)	7 (<1%)	20 (1%)
Grade 4 (potentially life-threatening)	0	0
Headache: Total	463 (13%)	391 (11%)
Grade 1 (no interference with activity)	343 (10%)	281 (8%)
Grade 2 (some interference with activity)	105 (3%)	89 (3%)
Grade 3 (prevents daily activity)	15 (<1%)	21 (1%)
Grade 4 (potentially life-threatening)	0	1
Fatigue: Total	466 (13%)	361 (10%)
Grade 1 (no interference with activity)	344 (10%)	254 (7%)
Grade 2 (some interference with activity)	109 (3%)	85 (2%)
Grade 3 (prevents daily activity)	13 (<1%)	22 (1%)
Grade 4 (potentially life-threatening)	0	1
Nausea: Total	101 (3%)	98 (3%)
Grade 1 (no interference with activity)	81 (2%)	72 (2%)
Grade 2 (some interference with activity)	14 (<1%)	21 (1%)
Grade 3 (prevents daily activity)	5 (<1%)	5 (<1%)
Grade 4 (potentially life-threatening)	1	0
Vomiting: Total	48 (1%)	59 (2%)

Subjects experiencing at least one systemic AE[1] by maximum intensity	Fluad N[2] = 3505 n[3] (%)	Agriflu N = 3495 n (%)
Grade 1 (no interference with activity)	33 (1%)	38 (1%)
Grade 2 (some interference with activity)	13 (<1%)	17 (<1%)
Grade 3 (prevents daily activity)	1 (<1%)	4 (<1%)
Grade 4 (potentially life-threatening)[4]	1	0
Diarrhea: Total	168 (5%)	158 (5%)
Grade 1 (no interference with activity)	111 (3%)	119 (3%)
Grade 2 (some interference with activity)	44 (1%)	30 (1%)
Grade 3 (prevents daily activity)	12 (<1%)	8 (<1%)
Grade 4 (potentially life-threatening)	1	1

Source: Adapted from BLA 125510/0.11 Clinical Study Report Tables 14.3.1.2.7 and 14.3.1.2.17

[1]AE: adverse event

[2]N: total number of subjects

[3]n: number of subjects per group

[4]Potentially life-threatening defined as those requiring an emergency room visit or hospitalization

Unsolicited Adverse Events

Unsolicited adverse events were captured at the Day 22 clinic visit. Sixteen percent of subjects in each of the vaccine groups reported at least 1 unsolicited AE, for which the specific types were similar and balanced between groups. The most commonly reported unsolicited AEs were nasopharyngitis (2% in both groups), headache (1% of Fluad recipients and 2% Agriflu recipients), and cough (1% in each group).

6.1.12.3 Deaths

A total of 52 (1.5%) Fluad recipients and 46 (1.3%) Agriflu recipients died during the study. Although no deaths occurred within 21 days three subjects in the Fluad group had events leading to death. One subject was diagnosed with heart disease, diabetes and pulmonary tuberculosis 12 days postvaccination and died 6 weeks later from the same; one subject had lung cancer diagnosed 18 days postvaccination and died 3 months later; one subject had acute cholecystitis diagnosed 12 days postvaccination and died 1 month later from an acute myocardial infarction in the setting of upper gastrointestinal bleeding. The investigators assessed these deaths as unrelated to study vaccination. Of note, one subject in the Agriflu arm died of Guillain-Barré syndrome 228 days postvaccination. Investigators reported 3 deaths in the Fluad arm and 4 deaths in the Agriflu arm as related to influenza, although none were microbiologically confirmed.

Reviewer comment: Deaths occurring in this elderly population were generally temporally remote from receipt of study vaccine and appeared balanced between vaccine arms, both in number and cause of death. No evidence for causality was idenitified upon review of the case narratives of deaths for which the adverse event began within 21 days of receipt of vaccine.

6.1.12.4 Nonfatal Serious Adverse Events

In both vaccine groups, 39 subjects (1% of the safety set) developed SAEs through study Day 22, most of which were moderate to severe in intensity (Table 24). The system organ class (SOC) with the largest number of subjects reporting an SAE was "infections and infestations", with 7 subjects in the Fluad group and 4 subjects in the Agriflu group, respectively, reporting such an event. The only AE within that SOC to be reported by more than 1 subject was pneumonia, in 3 subjects. In addition, 2 subjects and 3 subjects in the Fluad and Agriflu groups, respectively, reported SAEs in the SOCs "cardiac disorders" and "respiratory, thoracic, and mediastinal disorders".

Table 24. Subjects with SAE[1]s Through Day 22 by System Organ Class for Study V70_27

System Organ Class	Fluad N[2] = 3545 n[3] (%)	Agriflu N = 3537 n[3] (%)
Any Serious Adverse Event	19 (1%)	20 (1%)
Blood & Lymphatic System Disorders	1 (<1%)	1 (<1%)
Cardiac Disorders	2 (<1%)	3 (<1%)
Gastrointestinal Disorders	0	1 (<1%)
Gen. Disorders & Admin. Site Cond.	0	2 (<1%)
Hepato-Biliary Disorders	3 (<1%)	0
Infections & Infestations	7 (<1%)	4 (<1%)
Injury & Poisoning	1 (<1%)	2 (<1%)
Metabolism & Nutrition Disorders	3 (<1%)	0
Musculoskeletal, Connective Tissue & Bone Disorders	2 (<1%)	2 (<1%)
Neoplasms Benign/Malignant (Including Cysts/Polyps)	1 (<1%)	1 (<1%)
Nervous System Disorders	1 (<1%)	3 (<1%)
Respiratory, Thoracic & Mediastinal Disorders	2 (<1%)	3 (<1%)

Source: Original BLA 125510/0.11 Clinical Study Report Table 12.3.1.2-1

[1]SAE: serious adverse event

[2]N: total number of subjects

[3]n: number of subjects per group

6.1.12.5 Adverse Events of Special Interest (AESI)

To capture AESIs (listed below), MedDRA system organ class and preferred terms were used to search the database. AESIs were obtained from collection of data regarding new-onset chronic disease and SAEs for the 1 year study duration. Six percent of subjects in each group reported onset of new chronic disease during the study (see safety objectives in Section 6.1.1. The most commonly reported diseases were hypertension (47 [1%] Fluad recipients and 43 [1%] Agriflu recipients); Osteoarthritis (11 [<1%] in each group); hypercholesterolemia (10 [<1%] in each group); and type II diabetes mellitus (11 [<1%] Fluad recipients and 9 [<1%] Agriflu recipients).

No imbalances were noted with regard to AESIs. Overall 26 (0.8%) Fluad recipients and 21 (0.6%) Agriflu recipients experienced an AESI. The most common AESIs in both group by system organ class were musculoskeletal and connective tissue disorders (15 Fluad recipients and 7 Agriflu recipients), and Endocrine disorders (all hypothyroidism; 4 Fluad recipients and 9 Agriflu recipients). These data are reviewed further in the integrated summary of safety, Section 8.4.8.

AESI database search terms included:

6.1.12.6 Clinical Test Results

Ninety-seven Fluad recipients and 103 Agriflu recipients had complete blood counts, serum chemistries and liver function tests collected on study Day 1 prevaccination and Day 8 postvaccination. Laboratory values were normal in the majority of subjects. Although a few subjects had abnormal laboratory values, most of these subjects had a similar abnormal value at baseline prevaccination. Subjects who had ≥ grade 1 changes in lab values from baseline per the CBER toxicity grading scale are listed in Table 25.

Table 25. Subjects with ≥ Grade 1 Change in Safety Laboratory Parameters at Day 8 Postvaccination for Study V70_27

Laboratory parameter[1]	**Change from baseline (Day 1 to Day 8)**	**Fluad N[1] = 97 n[2]**	**Agriflu N = 103 n**
Alanine aminotransferase (ALT)	Normal to Grade 1 (1.1-2.5 x ULN[3])	1	1
Aspartate aminotransferase (AST)	Normal to Grade 1 (1.1-2.5 x ULN[4])	2	0
Hemoglobin	Normal to Grade 1[5]	10	2
Hemoglobin	Grade 1 to Grade 2[6]	2	2
Hemoglobin	Grade 2 to Grade 3	1	1
Platelets	Normal to Grade 1 (125-140 x 10^3/µL)	0	3
White Blood Cells	Normal to Grade 1 (2.5-3.5 x 10^3/µL)	4	4

Source: Original BLA 125510/0.11 Clinical Study Report Tables 12.4.2.1-2 and 16.2.8.4

[1]Only grades and parameters for which a new or worsening abnormality was noted are listed.

[1]N: total number of subjects

[2]n: number of subjects per group

[3]xULN: times upper limit of normal; ULN defined as 32 U/L for women and 35 U/L for men

[4]ULN defined as 34 U/L for women and 36 U/L for men

[5]Grade 1 defined as 11.0-12.0 g/dL for women and 12.5-13.5 g/dL for men or a 1.5g/L decrease from baseline.

[6]Grade 2 defined as 9.5-10.9 g/dL for women and 10.5-12.4 g/dL for men or a 1.6-2.0g/L decrease from baseline.

Reviewer comment: 13 Fluad recipients versus 5 Agriflu recipients were noted to have a decrease in hemoglobin at Day 8; accounting for this imbalance are the 10 subjects in the Fluad arm versus 2 in the Agriflu arm who had a mild decrease (normal to grade 1, which were abnormal

per parameters specified by the clinical lab used for the study but did not meet criteria per the toxicity grading scale). Although the explanation for this imbalance is unknown, it is reassuring that this trend was not noted for more severe values or larger decreases (i.e. normal to grade 2 or grade 3). No other imbalances are noted for changes in laboratory parameters from baseline.

6.1.12.7 Dropouts and/or Discontinuations

Of the 7082 subjects who were both vaccinated and included in the safety analysis set, 6717 completed the study (95% of vaccinated subjects). Of the 365 subjects who did not complete the study the most common reasons were lost to follow up (2% and 3% for Fluad and Agriflu respectively), death (1% in both groups), and withdrawal of consent (1% in both groups) (Table 26).

Table 26. Summary of Study Completion for Study V70_27

Population Description	Fluad	Agriflu
Enrolled Population	3552	3552
Vaccinated	3541 (99.6%)	3541 (99.6%)
Completed Study	3361 (95%)	3356 (94%)
Missing Primary Reason	1 (<1%)	0
Premature Withdrawals	190 (5%)	196 (6%)
Death[1]	51 (1%)	46 (1%)
AE	3 (<1%)	2 (<1%)
Withdrew consent	52 (1%)	43 (1%)
Lost to follow-up	73 (2%)	91 (3%)
Inappropriate enrollment	5 (<1%)	4 (<1%)
Administrative reason	1 (<1%)	1 (<1%)
Protocol deviation	2 (<1%)	2 (<1%)
Unable to classify	3 (<1%)	7 (<1%)

Source: Original BLA 125510/0.11 Clinical Study Report Table 10.1-1

[1]One subject (320/090) withdrew after developing an AE (lung neoplasm) that subsequently led to death; the death is not included in this table because the AE, rather than death, was the cause of the withdrawal.

6.1.13 Study Summary and Conclusions

Study V70_27 was a Phase III, randomized, controlled, multi-center, observer-blind study that enrolled 7109 subjects, to compare the safety and immunogenicity of Fluad with Agriflu in adults 65 years of age and older. Subjects were enrolled across 4 countries, balanced evenly between arms. Overall, 53% of subjects were from the Philippines, 30% of subjects were from the United States, 14% of subjects were from Columbia and 3% of subjects were from Panama.

Of the 7109 who were enrolled, 7104 were vaccinated of which 3541 each received Fluad or Agriflu. All subjects had blood drawn at Day 1 and Day 22 for evaluation of HAI titers. A subset of subjects had blood collected for evaluation of durability of immune response at 6 months and 1 year post vaccination (189 Fluad recipients and 191 Agriflu recipients); a subset of those

underwent safety laboratory testing at Day 1 and Day 8 (97 Fluad recipients and 103 Agriflu recipients).

The demographic characteristics were similar between the 2 study groups although they differed from the demographic distribution observed in the United States because 70% of subjects were from the Philippines, Colombia and Panama, where the demographic distributions are different from the United States.

The study met the first co-primary endpoint for lot equivalency of three lots of Fluad and then these data were pooled to assess immunologic noninferiority and then superiority. The second co-primary endpoint of immunologic noninferiority for all three vaccine strains was demonstrated for Fluad compared to Agriflu by GMT ratios and seroconversion rate differences. Immunologic superiority was demonstrated for A H3N2 Perth/2009 but not for A H1N1 California /2009 or Influenza B Brisbane/2008. The study did not meet success criteria for secondary immunogenicity or effectiveness endpoints.

Fluad recipients experienced increased local reactogenicity within 7 days of vaccination compared to Agriflu (48% versus 35%, respectively), mostly due to increased mild to moderate (grade 1 and 2) pain and tenderness at the vaccination site. Fluad recipients demonstrated increased systemic reactogenicity overall (32% versus 26% for Fluad and Agriflu, respectively). This was due to the cumulative effect of modestly increased systemic reactogenicity after Fluad in most categories (1-2% higher in the Fluad group for most categories except grade 1 myalgia [15% Fluad versus 10% Agriflu] and grade 1 fatigue [13% Fluad versus 10% Agriflu]). No imbalances in grade 3 local and systemic adverse reactions were noted. There were no imbalances in deaths, or other serious adverse events between the two study arms.

Using Day 22 HAI titers expressed as GMT ratios and seroconversion rate differences as a surrogate reasonably likely to predict clinical benefit Fluad demonstrated immunologic noninferiority in adults 65 years of age and older. Although Fluad demonstrated increased local and systemic reactogenicity within 7 days of vaccination, the increase was due mostly to differences at the grade 1 level, with no imbalances in grade 3 AEs noted. No imbalances in deaths SAEs or other important AEs were noted. Thus, the available safety and immunogenicity data support the accelerated approval of Fluad for the proposed indication of active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine in persons 65 years of age and older.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Forty-nine clinical studies conducted from 1992 through 2013 were submitted to this BLA for evaluation of safety with a focus on SAEs and AESIs (N= 27,787). It was agreed that data would be pooled in 8 groups, with some studies included in multiple groups, based on age, type of study design and vaccine formulation (Table 25). The duration of follow-up ranged from 3 weeks to 1 year post-vaccination. Thirty-six of these studies evaluated subjects who were > 65 years of age receiving their first-dose of Fluad; 8 studied subjects > 65 years of age; and 5 were extension studies (evaluating repeat annual dosing). Of the 36 studies in adults 65 years of age

and older, 15 were randomized controlled trials (RCTs), 17 were uncontrolled studies and 4 were bridging or stability studies. Over this time the vaccine formulation underwent changes from water to citrate buffer and from thimerosal-containing, to trace thimerosal-containing, and ultimately to thimerosal free.

Of the 15 RCTs in adults 65 years of age and older submitted to the BLA 7 of these studies (considered as 7 separate studies within the 49 total studies) went on to evaluate annual revaccination (5 studies evaluated a second annual dose and 2 studies evaluated a 3rd annual dose). Of note, the safety data from the phase 3 study V70_27 discussed separately in Section 6.1.12 are also included in the applicable pooled safety analyses (Table 27, pooling groups 1, 2, 3 and 5). The size of the Phase 3 study V70_27 was sufficient to quantify rates of solicited reactions for 7 days postvaccination. Thus, the primary goal of the integrated safety review was to identify potential new safety signals and to assess rates of SAEs, AESIs, or deaths and assess these for a causal association with administration of Fluad. The 15 RCTs will be described in detail in the ensuing sections 8.3 through 8.6. Review of the remaining 27 studies did not reveal new potential safety signals or rates of SAE or death that were inconsistent with that observed in RCTs or postmarketing surveillance. However, these studies will not be discussed further with the rationale for each presented below.

- 5 studies included only young adults and this age group will not be included in the proposed indication for this vaccine.
- 21 studies in the adults 65 years of age and older were uncontrolled. Thus, without a denominator evaluation for increased rates of adverse events (including SAEs and deaths) would not be possible.
- 1 phase 4 study conducted in Italy was excluded based on CBER request during pre-BLA discussions because, "the randomization [was] not clear, the vaccine used was not the intended formulation for licensure and phase 4 studies are intrinsically different in data collection".

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Table 27. Summary of Studies Used in Pooled Data for Integrated Safety Analyses

Pooling group	Trial characteristics	Parameters evaluated	Number of trials included	Number of subjects Fluad / TIV[1]
1	First-dose[2] trials conducted in elderly[3] subjects	Solicited and unsolicited AEs, SAE[4]s and AESI[5]s	36	7532[6] / 5198[7]
2	First-dose RCT[8]s conducted in elderly subjects (a subset of pooling group 1)	Solicited and unsolicited AEs, SAEs and AESIs	15	5754[6] / 5198[7]
3	First-dose RCTs conducted in elderly subjects with ≥ 180 Days follow up (a subset of pooling group 2)	SAEs and AESIs	10	4758[6] / 4690[7]

Pooling group	Trial characteristics	Parameters evaluated	Number of trials included	Number of subjects Fluad / TIV[1]
4	RCT revaccination studies in elderly subjects received additional doses of seasonal influenza vaccine (5 studies from pooling group 2 were extended for an additional 2 or 3 seasons)	Solicited AEs after first vaccination versus revaccination	5 (3 trials extended 1 season and 2 extended 2 seasons)	492 / 330
5	First-dose RCTs conducted in elderly subjects in which the citrate-buffered formulations of MF59 (with or without thimerosal) were the same as the product being evaluated in the current BLA (another subset of pooling group 2)	Safety and subgroup analyses the same as that of pooling group 1 except for exclusion of immediate post-vaccination events	7	4544[6] / 4375[7]
6	Uncontrolled studies in elderly (a subset of pooling group 1)	Evaluation of SAEs and AESIs	17	1005 (Fluad alone)
7	Phase 4 study in elderly subjects	SAE, AESI, immediate post-vaccination events and hospitalizations	1	9204 / 4557
8	Studies including healthy subjects < 65 years of age	SAEs, AESIs, and immediate post-vaccination events	8	744 / 552

Source: Adapted from BLA 125510/0.0: 5.3.5.3 Statistical Analysis Plan Version 5.0 Tables 4.1 and 4.2 and 5.2 Tabular Listing of All Clinical Studies.

[1]TIV: Trivalent influenza vaccine (unadjuvanted)

[2]First-dose: subjects receiving a first dose of Fluad, e.g. not those enrolled in extension studies evaluating repeat annual dosing.

[3]Elderly includes those ≥ 65 years of age

[4]SAE: serious adverse events

[5]AESI: adverse events of special interest, defined below in this Section under heading, "SAEs, Deaths, AE's Leading to Study Withdrawal, and Adverse Events of Special Interest"

[6]3545 of the subjects in this group were from the Fluad arm of the phase 3 study V70_27 serving as the primary basis for licensure (Section 6)

[7]3537 of the subjects in this group were from the Agriflu arm of the phase 3 study V70_27 serving as the primary basis for licensure (Section 6)

[8]RCT: randomized controlled trial

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 28. Demographic Characteristic for Subjects included in 15 Randomized Controlled Single-Dose Trials in Adults ≥ 65 Years of Age

Parameter	Fluad N = 5754	Agriflu N = 5198
Age (Mean ± SD; years)	72.9 ± 6.2	72.8 ± 6.2
Gender:		
Male	61.1%	62.9%
Female	38.9%	37.1%
Age Cohorts :		
65 - <75 years	66.0%	66.6%
>75 years	33.9 %	33.4%
Race:		
Asian	33.9%	37.5%
Black	1.3%	1.1%
Caucasian	64.5%	60.9%
Other	0.3%	0.4%
Missing	175	175
Ethnicity:		
Hispanic or Latino	11.5%	12.6%
Not Hispanic or Latino	88.5%	87.4%
Missing	175	175
Geographical location:		
United States	35.5%	32.3%
Outside the United States	64.5%	67.7%

Source: Adapted from BLA 125510/0.0: Section 5.3.5.3 Integrated Summary of Safety, Table 22

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The phase 3 study V70_27 provided the majority of the data obtained (Table 27). The remaining studies were small, (a range of 43 to 224 subjects per arm); the duration of follow up was varied (3-4 weeks in 11 studies, 8 weeks in 1 study, and 6 months in 3 studies); and the investigational products were varied (4 different formulations of Fluad and some used non-US licensed). Some data analyses, such as evaluation of AESIs, were conducted retrospectively for the pooled safety review.

8.4 Safety Results

8.4.1 Deaths

There were no imbalances noted either in overall deaths or in causes of death in the 15 randomized controlled single-dose studies in elderly subjects (Table 29).

Table 29. Summary of Deaths by System Organ Class and Preferred Term for More than 1 Subject for in 15 Randomized Controlled Single-Dose Trials in Adults ≥ 65 Years of Age

Cause of Death	aTIV[1] N[2] = 5754 n[3] (%)	TIV[4] N = 5198 n (%)
Number of Subjects With At Least One AE[5] Leading to Death	78 (1.4%)	81 (1.6%)
Cardiac disorders	36 (0.6%)	45 (0.9%)
Cardiac failure congestive	7 (0.1%)	13 (0.3%)
Myocardial infarction	8 (0.1%)	12 (0.2%)
Acute myocardial infarction	8 (0.1%)	5 (0.1%)
Cardiac failure	2 (<0.1%)	6 (0.1%)
Cardiac failure acute	3 (0.1%)	3 (0.1%)
Cardio-respiratory arrest	4 (0.1%)	0
Cardiac arrest	0	3 (0.1%)
Myocardial ischemia	3 (0.1%)	0
Atrial fibrillation	2 (<0.1%)	0
Cardiac disorder	2 (<0.1%)	0
Coronary artery disease	0	2 (<0.1%)
Infections and infestations	17 (0.3%)	11 (0.2%)
Pneumonia	9 (0.2%)	7 (0.1%)
Pulmonary tuberculosis	2 (<0.1%)	2 (<0.1%)
Septic shock	3 (0.1%)	1 (<0.1%)
Sepsis	2 (<0.1%)	1 (<0.1%)
Nervous system disorders	13 (0.2%)	13 (0.3%)
Cerebrovascular accident	6 (0.1%)	5 (0.1%)
Cerebrovascular disorder	3 (0.1%)	1 (<0.1%)
Cerebral hemorrhage	2 (<0.1%)	1 (<0.1%)
Hemorrhagic stroke	0	2 (<0.1%)
Neoplasms benign,	9 (0.2%)	8 (0.2%)
Gastric cancer	0	2 (<0.1%)
Metastatic neoplasm	2 (<0.1%)	0
Gastrointestinal disorders	4 (0.1%)	7 (0.1%)
Upper gastrointestinal	1 (<0.1%)	2 (<0.1%)
Respiratory, thoracic and mediastinal disorders	5 (0.1%)	4 (0.1%)
Respiratory failure	1 (<0.1%)	3 (0.1%)
General disorders and administration site conditions	5 (0.1%)	2 (<0.1%)
Multi-organ failure	3 (0.1%)	1 (<0.1%)
Renal and urinary disorders	3 (0.1%)	3 (0.1%)
Renal failure chronic	1 (<0.1%)	2 (<0.1%)

Cause of Death	aTIV[1] N[2] = 5754 n[3] (%)	TIV[4] N = 5198 n (%)
Vascular disorders	3 (0.1%)	2 (<0.1%)
Hypertension	2 (<0.1%)	1 (<0.1%)
Metabolism and nutrition disorders	2 (<0.1%)	2 (<0.1%)
Hepatobiliary disorders	2 (<0.1%)	0
Injury, poisoning and procedural complications	0	2 (<0.1%)

Source: Adapted from BLA 125510/0.0: Section 5.3.5.3 Integrated Summary of Safety, Table 46
[1]aTIV: MF59-adjuvanted trivalent influenza vaccine
[2]N: total number of subjects
[3]n: number of subjects in group
[4]TIV: trivalent influenza vaccine
[5]AE: adverse event

In the 7 revaccination studies, subjects randomized to the initial vaccine went on to receive a second annual dose of the same vaccine (5 studies) and then a 3rd annual dose of the same vaccine (2 studies) in a unblinded fashion. Subjects were followed for safety for 6 months postvaccination. The number of deaths occurring within 6 months and 2 or 3 annual doses are summarized below in Table 30. Of note, it was noted that in 1 study 8 deaths were observed in the aTIV arm versus no deaths in the comparator arm. This was a randomized controlled trial conducted in a nursing home in which the median age of the residents (in both groups was 85 years (versus 76 and 78 years of age (aTIV and TIV, respectively) for the pooled studies overall. It was noted that after the first dose of vaccine in this study that 11 subjects died in each arm; this study did not evaluate subjects after a 3rd annual dose. Table 31 shows the cause of death and temporal association to vaccination.

Table 30. Number and Percent of Deaths recorded in 7 revaccination studies conducted in Adults ≥ 65 Years of Age

Parameter	aTIV[1] (Dose 2) N[2] = 492 n[3] (%)	TIV[4] (Dose 2) N = 330 n (%)	aTIV (Dose 3) N = 150 n (%)	TIV (Dose 3) N = 87 n (%)
Death	17 (3.5%)	6 (1.8%)	0	0

Source: Adapted from BLA 125510/0.0: Section 5.3.5.3 Integrated Summary of Safety, Table 14.3.4.3
[1]aTIV: MF59-Adjuvanted trivalent influenza vaccine
[2]N: total number of subjects
[3]n: number of subjects in group
[4]TIV: trivalent influenza vaccine

Table 31. Evaluation of Cause and Timing of Deaths Postvaccination after a Second Annual Vaccination in 5 revaccination studies conducted in Adults ≥ 65 Years of Age

Parameter	aTIV[1] (Dose 2) N[2] = 492 n[3] (%) [postvaccination day or range]	TIV[4] (Dose 2) N = 330 n (%) [postvaccination day or range]
Congestive heart failure	7 (1%) [13 -183]	2 (0.6%) [40, 185]
Cardiac arrest	2 (<1%) [53, 63]	0
Acute myocardial infarction	2 (<1%) [35, 117]	0
Stroke	1 (<1%) [138]	0
Pneumonia	1 (<1%) [42]	0
Gastrointestinal bleed	0	2 (<1%) [36, 135]
Malignancy	2 (<1%) [101, 135]	0
Trauma	2 (<1%) [105, 139]	2 (0.6%) [2, 106]

Source: Adapted from BLA 125510/0.0: Section 5.3.5.3 Integrated Summary of Safety, Table 14.3.4.3

[1]aTIV: MF59-Adjuvanted trivalent influenza vaccine

[2]N: total number of subjects

[3]n: number of subjects in group

[4]TIV: trivalent influenza vaccine

Reviewer comment: Revaccination studies were conducted in a small number of subjects in an aging population. The imbalance noted is attributable to one study in which subjects were nursing home residents with multiple comorbidities and were on average older than the population as a whole. No imbalance in deaths was noted at year 1 or year 3 of these studies. Further, the manner of death and temporality to vaccination were both varied such that no pattern could be discerned or biologically plausible explanation to suggest a causal relationship.

8.4.2 Nonfatal Serious Adverse Events

In the 15 randomized controlled single-dose studies in elderly subjects 384 out of 5754 aTIV recipients (6.7%) and 366 out of 5198 TIV recipients (7.0%) experienced an SAE. Review of specific SAEs did not reveal imbalances in in cause of death with pneumonia being the most common (41 [0.7%] in aTIV recipients versus 42 [0.8%] in TIV recipients), followed by congestive heart failure (16 [0.3%] in aTIV recipients versus 26 [0.5%] in TIV recipients). Similarly no imbalances were noted in SAEs commencing within 30 days of vaccination (47 [0.8%] in aTIV recipients versus 57 [1.1%] in TIV recipients].

8.4.8 Adverse Events of Special Interest

AESI's were defined retrospectively using MedDRA preferred terms to search for events of potential immune etiology such as neuroinflammatory disorders (including narcolepsy by both a narrow and broad definition), rheumatological disorders, inflammatory bowel disease, thyroid disorders, inflammatory skin disorders, autoimmune hematologic disorders, and vasculitis (Table 32). No imbalances were noted overall (0.9% for both Fluad and the unadjuvanted comparator), by system organ class or by preferred term.

Table 32. Summary of AESIs[1] by Preferred Term in 15 Randomized Controlled Single-Dose Trials in Adults ≥ 65 Years of Age

Parameter	aTIV[2] N[3] = 5754 n[4]	TIV[5] N = 5198 n
Number of Subjects With At Least One AESI	48	48
Musculoskeletal and connective tissue disorders	24	16
Rheumatoid arthritis	7	3
Arthritis	15	12
Myositis	2	1
Vascular disorders	0	3
Thromboangitis obliterans	0	1
Arteritis	0	1
Temporal arteritis	0	1
Nervous system disorders	13	13
Radiculitis	3	7
Polyneuropathy	2	2
Neuritis	0	1
Radiculopathy	1	2
Sleep disorder	3	0
Encephalomyelitis	1	0
VII cranial nerve palsy	2	0
Somnolence	1	0
Guillain-Barré syndrome	0	1
Gastrointestinal disorders	2	1
Colitis	1	1
Crohn's disease	1	0
Endocrine disorders malignant and	4	10
Hypothyroidism	4	10
Blood and lymphatic system disorders	1	0
Idiopathic thrombocytopenia purpura	1	0
Respiratory, thoracic and mediastinal disorders	2	5
Sleep apnea	2	5
Skin and subcutaneous tissue disorders	2	0

Parameter	aTIV[2] N[3] = 5754 n[4]	TIV[5] N = 5198 n
Psoriasis	1	0
Erythema multiforme	1	0

Source: Adapted from BLA 125510/0.0: Section 5.3.5.3 Integrated Summary of Safety, Table 16.2.7.7

[1]AESI: adverse event of special interest

[2]aTIV: MF59-Adjuvanted trivalent influenza vaccine

[3]N: total number of subjects

[4]n: number of subjects in group

[5]TIV: trivalent influenza vaccine

[6]AE: adverse event

8.6 Safety Conclusions

Pooled safety analyses of 49 clinical studies submitted to this BLA revealed no new potential safety signals. Overall, no safety signals were observed when comparing aTIV to TIV were noted in SAEs, AESIs or deaths.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Though not directly relevant to the age indication for this application, the reproductive toxicity data submitted to this BLA support a Pregnancy Category B designation. This study evaluated 110 pregnant (b) (4) rabbits received either saline control or Fluad. No treatment-related effects were reported on pre-weaning physical or functional development of the kits, mortality, or necropsy assessment. Full details of this evaluation are contained in the toxicology review.

9.1.2 Use During Lactation

The safety of Fluad in women who are lactating has not been established.

9.1.3 Pediatric Use and PREA Considerations

The Pediatric Research Equity Act (PREA) requires that we consider the utility of studying Fluad in Pediatric age groups 0 through 16 years of age. A full waiver was requested by the Applicant for 0 through 16 years. For those ages 9 through 16 the rationale was based on the Code of Federal Regulations (CFR) Section 505B(a)(4)(B)(iii): the drug or biological product—(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is not likely to be used by a substantial number of pediatric patients in that age group. The Center for Biologics Evaluation and Research agreed with this proposal. For those ages 0 through 8 years studies were either planned or completed. For ages 0-6 months and 72 months through 8 years, studies were planned using the quadrivalent formulation of

Fluad (containing an additional influenza B strain) and it was proposed by the Applicant that these studies support both trivalent and quadrivalent formulations of Fluad. Since the product was quadrivalent, a waiver was requested by the Applicant for evaluation of the trivalent product in these age groups. For ages 6 through 71 months, a study using the trivalent formulation has been completed (and a study using the quadrivalent is planned as well) but the study report for the completed study was not available at the time of filing. While CBER agreed that the studies of the quadrivalent formulation would fulfill the PREA requirement for evaluation of Fluad in the pediatric groups 0 through 8 years of age, it was determined that this would constitute a deferral rather than a waiver, with the expectation that the full study reports would be provided upon study completion to support an indication in these pediatric populations. The Pediatric Review Committee (PeRC) concurred with these assessments.

9.1.4 Immunocompromised Patients

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

9.1.5 Geriatric Use

Fluad 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

Fluad met criteria for immunologic noninferiority against all three vaccine strains by Day 22 GMT ratios and seroconversion rate differences when compared with Agriflu, an unadjuvanted TIV. Local and systemic reactogenicity were higher for Fluad compared to Agriflu, however overall, safety is acceptable for approval.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 33. Summary of Risk-Benefit Analysis for Fluad

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Influenza virus infection is a major cause of morbidity and mortality • Older adults are a high-risk group for developing complications associated with influenza virus infection • Influenza vaccination has been shown to be effective in reducing the incidence of influenza-like illness (ILI), hospitalization for influenza/pneumonia/other respiratory conditions, acute complications among high-risk patients, and mortality from all causes	• Influenza virus infection is a potentially life-threatening disease • Influenza virus infection is a serious condition, particularly in older adults who are high-risk for developing complications including death

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Unmet Medical Need	• Older adults have decreased immunologic responsiveness to currently available influenza vaccines than younger adults. • Current Advisory Committee on Immunization Practice (ACIP) guidelines have expanded recommendations for annual seasonal influenza vaccination to include those who are pregnant, ≥ 50 years of age, between the ages of 6 and 59 months increasing the demand for influenza vaccines • Manufacturing delays and market withdrawals lead to vaccine shortages. CBER considers shortage of influenza vaccines to be ongoing.	• In older adults there is an unmet medical need for effective prevention of influenza • Vaccine shortages could lead to delays or lapses in annual vaccination in older adults
Clinical Benefit	• One clinical trial in adults 65 years of age and older conducted under IND (V70_27) demonstrated immunologic noninferiority compared to the US licensed comparator Agriflu with regard to Day 22 HAI titers expressed as GMT ratios and seroconversion rate differences. Fluad failed to meet the additional co-primary endpoint of immunologic superiority. The study failed to meet success criteria for secondary endpoints evaluating immunogenicity in subjects with chronic medical conditions and in all subjects against heterologous strains. It showed no important differences in antibody persistence or effectiveness	• Use of HAI titers is an acceptable surrogate marker reasonably likely to demonstrate clinical benefit as required for accelerated approval and demonstration of immunologic non-inferiority compared with Agriflu fulfills this requirement. • Prevention of influenza illness in the elderly reduces morbidity and mortality associated with influenza infection in the adults 65 years of age and older.
Risk	• The most substantial risks of vaccination with Fluad were mild local and systemic reactogenicity. • No other safety signals, including no notable imbalances in AESIs, were apparent in evaluation of pooled safety studies conducted outside of the United States • No other safety signals were identified in postmarketing surveillance across 38 countries reflecting approximately 85.1 million doses distributed since initial approval in 1997 (Italy)	• All the evidence indicates that the risk of vaccination with Fluad is acceptable

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• The most substantial risks of vaccination with Fluad are associated with the inflammation produced at the injection site. Erythema, swelling, and pain are very common. However, the most injection site reactions are mild in severity, and they resolve relatively quickly and 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 laboratory-confirmed influenza caused by any influenza viral type/subtype included in the vaccine. As the risks of vaccination with Fluad 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

Traditional approval could have been considered if a prospective, randomized, controlled trial, either evaluating either absolute or relative efficacy has been conducted as the basis for licensure. 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 those who would not otherwise be immunized during a shortage provides a meaningful benefit over the then-existing treatments, which are viewed by CBER as in short supply at that time (if all individuals for whom the vaccine is recommended were to be vaccinated). Trial V70_27 evaluated safety and immunogenicity using HAI titers as a surrogate for protection and had an appropriate trial design to support accelerated approval. Demonstration of clinical effectiveness is required post licensure and will be evaluated in the confirmatory efficacy trial V118_18.

11.4 Recommendations on Regulatory Actions

Fluad is recommended for accelerated approval, based on the surrogate of HAI 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

The package insert submitted by the applicant was in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006. CBER removed language regarding mechanism of action for the adjuvanted product because it was viewed as promotional. CBER removed language regarding the impact of Fluad versus Agriflu on immunogenicity with respect to heterologous strains and antibody persistence due to both limitations in study design and the

results (See section 6.11.1.2). Revisions to the label were agreed upon by the Applicant and CBER.

Please note, the Applicant was asked to include the range of subjects for each event listed in the Table 1 that describes local and systemic adverse reactions, whereas the total number of subjects evaluated was used in this review. All numbers were verified for the both label and the review.

11.6 Recommendations on Postmarketing Actions

No changes to the submitted pharmacovigilance plan for Fluad 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. The Applicant has proposed V118_18, an absolute efficacy trial comparing an MF59-adjuvanted quadrivalent inactivated seasonal influenza vaccine (aQIV) produced using the Agriflu manufacturing process with an active control Tdap vaccine, (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed [Boostrix®]), in adults $\geq$ 65 years of age. This study has been reviewed by CBER and will have begun at the time of approval. Because the Applicant is not making claims of superiority, an absolute efficacy study rather than a relative efficacy trial comparing aQIV with another seasonal influenza vaccine is acceptable.