Summary Basis of Regulatory Action
(SBRA)

Date: November 23, 2015

From: Brenda R. Baldwin, Ph.D., Chair of the Review Committee

BLA/ STN: 125510/0

Applicant Name: Novartis Vaccines and Diagnostics

Date of Submission: November 25, 2014

Submission PDUFA Goal Date: November 25, 2015

Proprietary Name: Fluad

Proper Name: Influenza Vaccine, Adjuvanted

Indication: Influenza Vaccine, Adjuvanted is indicated for active immunization against disease caused by the influenza subtypes A and type B contained in the vaccine. Influenza Vaccine, Adjuvanted is approved for use in persons 65 years of age and older.

Recommended Action: Approval

Signatory Authorities Action: Approval

Office Signatory Authority: Marion F. Gruber, Ph.D., Director, Office of Vaccine Research and Review

☐ **I concur with the summary review.**
☐ **I concur with the summary review and include a separate review to add further analysis.**
☐ **I do not concur with the summary review and include a separate review.**

Specific Documentation Used in Developing the SBRA	**Reviewer Name – Document(s) Date**
Clinical Review	Sarah K. Browne, M.D. – November 20, 2015
Pharmacovigilance Review	Yandong Qiang, M.D., Ph.D., M.P.H., M.H.S. – August 22, 2015 Maria Said, M.D. – November 16, 2015
Statistical Review, Clinical	Ghideon Solomon, Ph.D. – November 4, 2015
Statistical Review, Bioassay	Zhong Gao, Ph.D. – November 6, 2015
Bioresearch Monitoring Review	Anthony Hawkins, M.S. – August 31, 2015
Product Review	Marina Zaitseva, Ph.D. (Adjuvant CMC Review) – October 8, 2015 Hang Xie, Ph.D. (Antigen CMC Review) – October 23, 2015 Ira Berkower, M.D. (Agriflu CMC Review from STN 125297/0) – October 14, 2009
Labeling Review	Sonny Saini – July 29, 2015 Sarah Browne, M.D. – November 20, 2015 Kirk Prutzman, Ph.D. – November 20, 2015
Testing Method and Analytical Chemistry	Manju Joshi, Ph.D. – October 1, 2015 Alfred Del Grosso, Ph.D. – November 3, 2015 Simleen Kaur, M.S. – July 13, 2015
Testing Results	Hyesuk Kong, Ph.D. – October 28, 2015 Manju Joshi, Ph.D. – October 1, 2015 Alfred Del-Grosso, Ph.D. – October 26, 2015
Lot Release Protocol Template	Josephine Resnick, Ph.D. – October 30, 2015
Toxicology Review	Nabil Al-Humadi, Ph.D. – November 13, 2015
Inspection Waiver Memo	Pankaj Amin – October 22, 2015
Establishment Review	Pankaj Amin – November 16, 2015
Categorical Exclusion Memo	Pankaj Amin – November 16, 2015

1. Introduction

Influenza Vaccine, Adjuvanted, also known as Fluad, is indicated for active immunization against disease caused by the influenza subtypes A and type B contained in the vaccine. Influenza Vaccine, Adjuvanted is approved for use in persons 65 years of age and older.

Fluad consists of an inactivated, subunit trivalent influenza virus antigen produced in eggs and an oil-in-water emulsion adjuvant (MF59C.1 adjuvant). The antigen in Fluad is manufactured in (b) (4) ., according to the Agriflu seasonal influenza virus vaccine process licensed in the United States (U.S.). The MF59C.1 adjuvant in Fluad is manufactured at a Novartis' facility in (b) (4) . The MF59C.1 adjuvant contains one biodegradable oil, squalene, mixed with an aqueous phase consisting of sodium citrate dehydrate and citric acid monohydrate. Polysorbate 80 and sorbitan trioleate are used as surfactants to stabilize the oil/water interface. The final drug product containing the antigen and adjuvant is combined and filled at the (b) (4) facility.

Fluad is an emulsion for intramuscular injection supplied in a 0.5 mL single-dose pre-filled syringe. Each 0.5 mL dose contains:

- 45 micrograms (mcg) hemagglutinin (HA) of influenza – 15 mcg of each influenza subtype (A/AH1N1, A/H3N2 and B)
- 9.75 mg squalene
- 1.175 mg sorbitan trioleate
- 1.175 mg polysorbate 80
- 0.66 mg sodium citrate dihydrate
- 0.04(b) (4) mg citric acid monohydrate

Each 0.5 mL dose may also contain residual amounts of neomycin(b) (4) 0.02 mcg by calculation), kanamycin (b) (4) 0.03 mcg by calculation), barium (< 0.5 mcg by calculation), egg proteins (b) (4) 0.4 mcg), formaldehyde (≤ 10 mcg) and cetyltrimethylammonium bromide (CTAB) (≤ 12 mcg) from the antigen manufacturing process. The vaccine does not contain preservative. The proposed shelf life is 12 months at 2 to 8^{o}C and the date of manufacture is defined as the date of initiation of final drug product formulation.

2. Background

For seasonal influenza vaccines, an approval pathway under the accelerated approval regulation (21 CFR § 601.41) is an option described in the May 2007 Food and Drug Administration (FDA) Guidance for Industry titled "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines." Accelerated approval will be based on adequate and well-controlled clinical trials establishing that the biological product is safe and has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Approval under this regulation will be subject to the requirement that the sponsor study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit. Postmarketing trial(s) must also be adequate and well-controlled and should be conducted with due diligence [1].

CBER held a pre-BLA meeting with Novartis on December 16, 2011, and a type C meeting on September 20, 2013, to discuss the manufacturing, pre-clinical and clinical information to be included in a BLA submission for Fluad. CBER agreed that immunogenicity and safety data from clinical trial V70_27, as well as safety data from other studies, could be considered to support an approval under the accelerated approval regulation.

On November 25, 2014, Novartis submitted a BLA for Fluad to CBER, FDA. This BLA was denoted STN 125510. The PDUFA Action Due date is November 25, 2015.

The BLA submission includes immunogenicity and safety data from one phase 3 clinical trial conducted under IND 14368; the trial is V70_27 conducted in adults 65 years of age and older. The BLA also includes supportive safety data from other studies conducted in adults 65 years of age and older and a small proportion of adults 18 to 64 years of age. The data accrued from trial V70_27 fulfilled the immunogenicity criteria to support licensure of Fluad under the accelerated approval regulation.

Novartis originally proposed a proprietary name of Fluad 65 for the seasonal trivalent influenza vaccine. CBER initially accepted the name with concern; however, upon further consideration, CBER recommended revising the proper name to "Fluad" because the "65" was deemed promotional and the proposed name for a possible quadrivalent formulation would be problematic if also approved for use in other age groups in the future. Novartis concurred with this revision to the proprietary name.

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 $\geq$ 12 years of age and children 6 months to < 2 years of age, respectively.

3. Chemistry Manufacturing and Control (CMC) Information

a) Product Quality

The information provided in the BLA for Fluad demonstrates that the manufacturing process is well controlled with appropriate validations. Moreover, adequate quality control testing has been conducted and stability data have been accrued with Fluad. Fluad is supplied as a 0.5 mL single-dose, pre-filled glass syringe of inactivated, subunit, trivalent influenza antigen in suspension with MF59C.1 adjuvant.

Components of the Fluad Vaccine

As agreed by CBER (Type C Meeting on September 20, 2013), (b) (4) of the CMC sections from the Agriflu BLA (STN 125297) that describe the U.S. licensed Agriflu Drug Substance (DS) was included in the current Fluad BLA for (b) (4) produced in (b) (4) and that produced in (b) (4). The (b) (4) site is no longer intended for MPH production or testing, but is included in the current Fluad BLA as part of the development history of Agriflu. During the review of this BLA, the Agriflu DS manufacturing process was changed to (1 (b) (4)

(b) (4) . These changes in the Agriflu BLA (125297/supplement 68 and 69) were approved on September 3, 2015, and the relevant information was incorporated into this Fluad BLA. Also during the review, Novartis proposed to change the final vaccine release site from (b) (4) . Novartis indicated that there were no changes proposed to the release testing assays/equipment but only a transfer of release activity (e.g., review of batch production records, etc.) from (b) (4) . Because all of the tests and manufacturing activities remained the same, CBER agreed.

The A/H1N1, A/H3N2 and B antigen included in the trivalent vaccine are recommended each year by the World Health Organization (WHO) and FDA's Vaccines and Related Biological Products Advisory Committee.

Antigen Drug Substance (DS) - MPH

The antigen DS consists of a (b) (4) purified influenza virions propagated in embryonated chicken eggs. (b) (4) culture, harvest, and inactivation of the influenza virus (b) (4) using formaldehyde treatment. (b) (4)

Control of Materials Critical elements of the product information included in the BLA are related to the inactivation of the influenza virus, determination of the HA potency for formulation, validation of the manufacturing process for the final vaccine product, development of appropriate quality control testing plan to ensure manufacturing consistency and final container product quality, and stability data to support the hold times for intermediates and bulks and to support the requested dating period for the product once released for market distribution. Data and information included in the BLA demonstrate that the manufacturing process is well controlled. (b) (4) .

Production Strain History: Based on guidance provided by the WHO Collaborating Centers, the reference strain (candidate vaccine virus) is selected. The A strains are derived by co-infection of the original isolate with a lab adapted strain to produce a reassortant virus expressing the desired HA and NA proteins. Other genes present in the reassortant are derived from a human influenza virus A/PR/8/34, which is widely used as a backbone to construct strains for seasonal influenza virus vaccines. Influenza B strains are generally not reassortants.

2 pages determined to be not releasable: (b)(4)

(b) (4)

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Drug Product (DP)

In order to manufacture the DP final bulk (FB), the required amount of each sterile MPH DS that is necessary to achieve the target HA concentration is added into (b) (4)

(b) (4)

Controls for FB Production: A successful FB formulation depends on pH (b) (4) tests which indicate if there is any error in the weighed quantities and in the mixing process.

Stability of Final Bulk: The DP FB may be (b) (4)

Specifications and testing methods: The proposed specifications and testing methods for the routine control of Fluad DP (b) (4) FC are shown in Table 2.

Table 2. Tests, Methods, and Specifications for Quality Control Release of the Fluad Drug Product Final Bulk and Final Container and Packed Product

Test (Method)	**Fluad Drug Product Final Bulk Specifications**	**Fluad Drug Product Final Container Specifications**
HA Identity ((b) (4)	(b) (4)	Positive
HA Content (Single Radial Immunodiffusion)	(b) (4)	(b) (4)
Squalene Identity (b) (4)	(b) (4)	Positive
Squalene (b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Total Protein (b) (4)	(b) (4)	N/A

Test (Method)	**Fluad Drug Product Final Bulk Specifications**	**Fluad Drug Product Final Container Specifications**
Other Proteins than HA (calculation)	(b) (4)	N/A
Appearance (Visual Inspection)	(b) (4)	Milky white emulsion
Visible Particles (b) (4))	(b) (4)	Absence of visible particles after shaking
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
pH ((b) (4)	(b) (4)	Between 6.9 and 7.7
(b) (4) (b) (4)	(b) (4)	(b) (4)
Formaldehyde Content (b) (4))	(b) (4)	(b) (4)
Ovalbumin Content (b) (4)	(b) (4)	(b) (4)
CTAB (b) (4)	(b) (4)	(b) (4)
Sterility (b) (4)	(b) (4)	Absence of growth
Sterility (b) (4)	(b) (4)	Absence of growth
Viral Inactivation (b) (4)	(b) (4)	(b) (4)

Test (Method)	Fluad Drug Product Final Bulk Specifications	Fluad Drug Product Final Container Specifications
Endotoxin Content (b) (4)	(b) (4)	(b) (4)
Extractable volume ((b) (4)	(b) (4)	(b) (4) 0.50 mL

(b) (4) = International Unit;
N/A = not applicable

Because CBER performs influenza vaccine release tests on the DP FB, we requested that Novartis include tests already performed on the DP FC as part of the DP FB tests to facilitate expeditious release of product. These tests which are now added to the DP FB (table 2 above) include (b) (4) .

Endotoxin Specification: The release specification is based on the process capability data and not on CBER's reference lot (b) (4)

Exemption from the General Safety Test (GST): Novartis requested exemption from the GST for the DP FC. CBER indicated that since the final rule for revocation of the GST became effective on August 3, 2015, Novartis is not required to conduct the GST.

Final Container: The filling process validation was performed on (b) (4) syringes. All Fluad batches assessed for the validation of the filling process were within the acceptance criteria for HA content and squalene strength, confirming that the filling process consistently produces homogeneous batches of DP. A risk assessment determined that the validation of the (b) (4) syringes supports the planned usage of the LL syringe for the US market. The current filling process requires access with gloved portals. A media fill run performed with (b) (4) syringes on (b) (4) demonstrated that all tested syringes passed the acceptance criteria of sterility and fertility (growth promotion). The packed product release test includes HA identity by (b) (4). Table 3 shows the composition of the Fluad DP FC per 0.50 mL dose.

Table 3. Quantitative Composition of the Drug Product Final Container per 0.50 mL Dose

INGREDIENTS	QUANTITY per 0.50 mL	FUNCTION
Antigen: Split-virion Monovalent, A/H1N1, A/H3N2 and B	45 µg HA (15 µg/each)	Antigen

INGREDIENTS	QUANTITY per 0.50 mL	FUNCTION
Adjuvant: MF59C.1		
Squalene	9.75 mg	Oil
Polysorbate 80	1.175 mg	Surfactant
Sorbitan Trioleate	1.175 mg	Surfactant
Sodium Citrate	0.66 mg	Buffer
Citric Acid	0.04 mg	Buffer
(b) (4)	(b) (4)	(b) (4)
(b) (4)		

Overages: To allow withdrawal of the nominal volume (0.5 mL) of the Fluad vaccine, the DP FC syringe will contain an overfill of up to (b) (4) (target volume is (b) (4) An overage of up to (b) (4) of the HA concentration is included for each virus strain (exact amount varies year to year) to assure the potency specification can be met for the 12-month shelf-life.

Residuals: Fluad in single dose pre-filled syringe may contain trace amounts of neomycin (≤ 0.02 µg by calculation), kanamycin (≤ 0.03 µg by calculation), barium (< 0.5 µg by calculation), formaldehyde (≤ 10 µg) and CTAB (≤ 12 µg) which are used in the process of DS (MPH), as well as residual amounts of egg protein-ovalbumin (< 0.4 µg). Due to the presence of the emulsion adjuvant MF59C.1, which confounds the formaldehyde test result, the amount of residual formaldehyde could not be tested at the (b) (4) stage. The estimate is based on the release specification of residual formaldehyde at the (b) (4) level and the detection limit of formaldehyde in the Agriflu (b) (4)

Potency Evaluation: The Single Radial Immunodiffusion (SRID) assay is used to measure HA content of the antigen component of the Fluad vaccine. For final lots destined for the US market, the SRID testing is performed by Novartis using CBER reagents and evaluated using the parallel line method in accordance with US release specifications. Validation confirms that the presence of MF59C.1 adjuvant has no impact on the accuracy of SRID testing. Novartis thus states that all future SRID validation/verification studies will be performed with reference antigen which is reconstituted in water only and sample dilutions performed with (b) (4) instead of diluted MF59C.1. This was found acceptable by the antigen reviewer.

Extractables/Leachables: The primary container for Fluad is a (b) (4) syringe (b) (4) and (b) (4) plunger (b) (4) - with no needle attached. No safety concerns were evident in an extractable study and 12 month leachable study performed in these syringes.

Dating Period Evaluation: The proposed dating period for Fluad DP FC is 12 months from the date of formulation when stored at 2°C to 8°C, protected from light. Novartis proposes to place three lots of Fluad DP FC in LL syringes stored (b) (4) from each flu season into the ongoing stability program at 2°C to 8°C for up to (b) (4) months with the sampling time points at 0, 3, 6, 9, 12, (b) (4) months. The evaluation consists of the following parameters: appearance, pH, HA content, sterility, container closure integrity test (CCIT), squalene, (b) (4), visible particles, as well as endotoxin. At least (b) (4) lot from each season will be tested under accelerated stability program at (b) (4) Novartis conducted the container closure integrity testing, using a (b) (4) test method and all acceptance criteria were met.

Cartons/Containers: Fluad is pre-filled into 0.5 mL single dose syringes. The syringes are labeled and packaged into a grouping box (carton) that contains 10 syringes in a blister pack. Final cartons of Fluad are stored at 2°C to 8°C until release and shipment for distribution.

b) CBER Lot Release

The final Lot Release Protocol (LRP) template for Fluad was submitted to CBER for review on October 16, 2015, under amendment 26, and it was found acceptable. The LRP template includes all release tests performed on each monovalent pooled harvest, as well as the formulated trivalent bulk with the MF59 adjuvant. Samples and the results of the tests from at least three, but not more than five lots of monovalent pooled harvests from each of the 3 strains of influenza virus will be submitted to CBER for testing at the beginning of each new influenza season. Samples and final protocols with results for the formulated trivalent bulks containing the MF59C.1 adjuvant will be submitted to CBER for lot release. CBER will only release the formulated trivalent bulk lots containing MF59C.1 adjuvant. Safety and purity of each lot of the vaccine submitted to CBER will be evaluated from the information provided in the LRP and by confirmatory CBER testing. In addition, each new virus seed will undergo the HAI test to confirm identity.

Because Novartis indicated that they would not be launching any lots for the 2015/2016 influenza season, CBER allowed Novartis to submit for testing one lot of each antigen monovalent bulk from the 2014/2015 influenza season and three lots of bulk formulated vaccine derived from the three monovalent bulks and representing the manufacturing process described in the BLA. Three Fluad lots were provided on September 3, 2015, for in-support testing and were found to be acceptable. The Fluad lots were manufactured with the (b) (4) . After internal discussion, it was agreed that lots made with this latest change could still be used for CBER's confirmative testing; however, this change could not be incorporated into the BLA.

c) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be acceptable. The facilities involved in the manufacture of Fluad are listed in table 4 below. The activities performed and inspectional histories are also noted in table 4.

Table 4: The following facilities are responsible for the manufacture of Fluad:

Name/address	FEI number	DUNS number	Inspection/ waiver	Justification/ Results
Manufacture of the master and working seeds, manufacture of the MPH drug substance, in-process and release testing of drug substance. Novartis Vaccines and Diagnostics LTD (b) (4)	(b) (4)	(b) (4)	Inspection Waived	Team Biologics, (b) (4) VAI
Manufacture of drug product Quality Control Testing, Batch Release. Novartis Vaccines and Diagnostics (b) (4)	(b) (4)	(b) (4)	Inspection Waived	Team Biologics, (b) (4). VAI
In-process and release testing of drug substance Novartis Vaccines and Diagnostics (b) (4)	(b) (4)	(b) (4) 1	Inspection Waived	Team Biologics, (b) (4) VAI

CBER waived the requirement to perform pre-license inspections based on the compliance history of the facilities used in the manufacture of Fluad. Team Biologics performed surveillance inspections of the facilities as indicated above in table 4. All FDA 483 issues were resolved and the inspections were classified as voluntary action indicated (VAI). An inspection waiver was not requested for the facility in (b) (4) that manufactures MF59C.1 adjuvant because the adjuvant is added to the final bulk formulation as a component after sterile filtration at the (b) (4) facility.

d) Environmental Assessment

A request for a Categorical Exclusion from an Environmental Assessment under 21 CFR § 25.31(c) was submitted to the BLA. The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Pre-clinical toxicity studies were conducted in order to identify and evaluate any toxicity findings following the administration of Fluad. These included GLP-compliant toxicology studies to evaluate the vaccine formulation considered in this BLA, as well as related investigational MF59-adjuvanted influenza virus vaccines, administered intramuscularly in local tolerance, single dose toxicity and repeat dose toxicity studies in rabbits. Vaccination of rabbits with MF59-adjuvanted influenza virus vaccines caused a slight inflammation locally at the injected muscle. Systemically, a few hematology and clinical chemistry parameters related to the local inflammation were transiently affected. The inflammation was diminished in the recovery animals. These studies did not reveal significant safety issues.

A reproductive and developmental toxicity study performed in female rabbits revealed no evidence of impaired female fertility or harm to the fetus due to vaccination with Fluad. In this study, the effect of Fluad on embryo-fetal and pre-weaning development was evaluated. Rabbits were administered Fluad by intramuscular injection twice prior to gestation (21 and 7 days before mating), and during the period of organogenesis (gestation days 7 and 20), at the proposed human dose of 0.5 mL/dose/rabbit (approximately 30-fold excess relative to the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis. Based on the conclusions drawn from this study, Fluad received a Pregnancy Category B designation and this is reflected in the package insert (PI) under Section 8.1. *Pregnancy*.

Genotoxicity studies were conducted using several *in vitro* assays to evaluate the mutagenic activity of MF59 adjuvant alone. No mutagenic effects were observed in the Ames assay. MF59 adjuvant was also tested *in vivo* in a mouse micronucleus cytogenetic test and no effect was observed in this assay.

Overall, based on the nonclinical toxicology assessments provided in the submission, CBER concluded that there are no significant safety issues to preclude the BLA from being approved.

5. Clinical Pharmacology

No clinical pharmacology or pharmacokinetic studies were performed as part of the clinical development program for Fluad.

6. Clinical/Statistical

As mentioned previously, the antigen suspension of Fluad is manufactured according to the same process as that used to produce the antigens contained in Agriflu, a U.S.-licensed seasonal influenza virus vaccine. The effectiveness of Fluad was inferred from serum hemagglutination inhibition (HAI) antibody responses induced by vaccination with Fluad.

Novartis conducted one phase 3 clinical trial, V70_27 (NCT01162122), and submitted immunogenicity, safety and reactogenicity data from 7,104 subjects in this trial (in which 3,552 subjects received the commercial formulation of Fluad) in support of the BLA for Fluad.

V70_27 was a randomized, observer-blind, multi-center, active-controlled trial designed to evaluate the immunogenicity and safety of one dose of Fluad administered intramuscularly (IM) to adults 65 years of age and older as compared to the unadjuvanted vaccine, Agriflu, to support licensure of Fluad. Trial V70_27 was conducted in 2010/2011 at 38 sites, 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. In this trial, 7,104 adult subjects ≥ 65 years of age were randomized 1:1, and stratified by age (65 through 75 years, and 76 years and older) to receive either Fluad (N = 3,552) or an active control, Agriflu (N = 3,552). The enrolled subject population was 65 to 97 years of age (mean 72 years) and 64% were female. 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, and the most commonly reported neurological/ neuromuscular or metabolic conditions including diabetes mellitus.

The immunogenicity of Fluad in V70_27 was assessed using endpoints and criteria described in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines." For a non-inferiority immunogenicity trial, the upper bound of the two-sided 95% confidence interval (CI) on the ratio of the geometric mean titers (GMTs) ($GMT_{\text{US licensed vaccine}}$/ $GMT_{\text{new vaccine}}$) should not exceed 1.5, and the upper bound of the two-sided 95% CI on the difference between seroconversion (SC) rates ($SC_{\text{US licensed vaccine}} - SC_{\text{new vaccine}}$) should not exceed 10 percentage points.

The HAI assay was used to detect HAI antibodies in serum samples from trial participants. The HAI assay used for the evaluation of clinical trial specimens was adequately validated and was performed using appropriate controls; however, Novartis was required to recalculate the original results because the HAI titer was determined using the volume of the serum plus virus, instead of CBER's requirement for titer being based on the original serum dilution added per well. This recalculation 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.

The primary immunogenicity objectives to be analyzed in a stepwise fashion were lot-to-lot consistency, non-inferiority, and then superiority of Fluad over Agriflu for homologous strains at Day 22. Lot-to-lot consistency was met if three consecutively manufactured final formulated bulk lots of vaccine elicited equivalent immune responses at Day 22 where the 2-sided 95% CI on the GMT ratio is within 0.67 and 1.5. Non-inferiority criteria were met if the lower bound of the 95% CI for the difference in SC rates (Fluad-Agriflu) and GMT ratios (Fluad/Agriflu) were > -10% and > 0.67, respectively. Superiority criteria were met if the lower bound of the 95% CI for the difference in SC 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 non-inferiority relative to Agriflu were met for both healthy (Table 5) and high risk subjects. Immunologic superiority of Fluad compared to Agriflu was demonstrated for only one of the three influenza vaccine strains (H3N2) and thus the primary endpoint of superiority was not met.

Non-inferiority of Fluad to Agriflu for 3 heterologous strains selected by the Applicant was evaluated as a secondary objective. The 3 strains were not predefined and were selected by Novartis without CBER input and thus no inference on heterologous protection can be made. The durability of immune response against the vaccine strains was also evaluated in a subset of patients (189, Fluad; 191 Agriflu) at 6 months and 1 year post vaccination as a secondary objective with results indicating an overall decline of the antibody responses relative to Day 22 titers for all 3 vaccine strains. Clinical efficacy against influenza-like illness, not microbiologically confirmed, was evaluated as another secondary endpoint. There was no significant difference in the clinical effectiveness observed between vaccine groups after a single dose, in terms of the incidence of influenza-like illness (ILI), exacerbation of preexisting chronic conditions, healthcare utilization, or mortality in the 12-month follow-up period.

Table 5: Post-vaccination Antibody Immune Responses by HAI at Day 22, Trial V70_27, Non-inferiority Comparison[4]

Strain	Fluad GMT[1] Seroconversion[2] (95% CI)[3]	Agriflu GMT Seroconversion (95% CI)	GMT Ratio Fluad/Agriflu Difference in Seroconversion Rate (95% CI)
A California H1N1/2009	99 (93-106) 69% (67-70%)	70 (66-75) 58% (57-60%)	1.41 (1.32, 1.49) 9.8% (7.5-12.1%)
A Perth H3N2/2009	272 (257-288) 73% (71-74%)	169 (159-179) 58% (56-60%)	1.61 (1.52, 1.70) 13.9% (11.7-16.1%)
B Brisbane/2008	28 (26-29) 33% (31-35%)	24 (23-26) 29% (28-31%)	1.15 (1.08, 1.21) 3.2% (1.1-5.3%)

[1] GMT is the Geometric Mean Titer
[2]Seroconversion is defined as the percentage of subjects with either pre-vaccination HAI < 1:10 and post vaccination HAI $\geq$ 1:40 or pre-vaccination $\geq$ 1:10 and post-vaccination 4-fold rise
[3]CI: Confidence Interval
[4] Number of subjects in the per protocol set (PPS) with available data is 3225-3227 for Fluad and 3256-3259 for Agriflu

Overall, Trial V70_27 demonstrated the following:

- Fluad elicits an immune response that fulfills CBER's criteria to support an accelerated approval of seasonal influenza vaccines after administration of one dose.
- The three consecutive lots of Fluad showed immunologic equivalence (lot consistency) in subjects 65 years of age and older.
- The immunogenicity of Fluad is non-inferior to the unadjuvanted vaccine (Agriflu).
- The immunogenicity of Fluad is not superior to the unadjuvanted vaccine (Agriflu).

Bioresearch Monitoring Review: The Bioresearch Monitoring Branch issued inspection assignments on February 20, 2015, covering three clinical investigators and trial sites for Protocol V70_27. The Bioresearch Monitoring inspection results from the aforementioned study sites did not reveal problems that impacted the data submitted in the BLA (Table 6).

Table 6. Inspections of Clinical Sites and Outcome

Study site #	Location	Enrolled subjects	Form FDA 483 issued?	Final inspection classification
326	Raleigh, NC	110	No	NAI*
332	Winston-Salem, NC	95	No	NAI

Study site #	Location	Enrolled subjects	Form FDA 483 issued?	Final inspection classification
206	Bogota, Colombia	640	No	NAI

*NAI = No Action Indicated

Pediatric Research Equity Act: A presentation of Novartis' Pediatric Plan was made to the FDA Pediatric Review Committee (PeRC) on September 30, 2015. The committee agreed with the recommendation for deferral of submission of trials for children aged 0 years through < 9 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed, and for a waiver for children aged 9 years to < 17 years for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for persons in this age group and is not likely to be used by a substantial number of persons in that age group. The Pediatric Research Equity Act (PREA) required studies specified in the approval letter and agreed upon with Novartis are as follows:

a. Deferred pediatric trial V118_05 under PREA to evaluate the efficacy, safety and immunogenicity of Fluad (aQIV) when administered to children 6 to < 72 months of age.

b. Completed pediatric trial V70_29 under PREA to evaluate the safety and immunogenicity of Fluad when administered to children 6 to < 72 months of age.

c. Deferred pediatric trial V118_19 under PREA to evaluate the safety and immunogenicity of Fluad (aQIV) when administered to children 6 to < 9 years of age.

d. Deferred pediatric trial V118_14 under PREA to evaluate the safety and immunogenicity of Fluad (aQIV) when administered to infants < 6 months of age.

7. Clinical Safety

The one phase 3 clinical trial, V70_27, and data from an additional 49 supportive studies, conducted in adults ≥ 65 years of age and a small proportion of adults 18 to 64 years of age between 1992 and 2013 (N=27,787) contributed to the safety database for Fluad.

In V70_27, the safety analysis set included 3,545 Fluad recipients and 3,537 Agriflu recipients. 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 severe adverse events (AEs) were balanced between arms for both solicited local and systemic reactions and comprised < 1% of subjects across all categories. Local reactions were reported by 35% and 20% of recipients, and systemic reactions were reported by 32% and 26%, respectively. The most common solicited adverse reactions were injection site pain and tenderness, myalgia, headache and fatigue. In the Fluad group, one subject had Grade 4 diarrhea and one subject had chills, nausea and vomiting (all Grade 4). Each of three subjects in the Agriflu group had one Grade 4 event which was headache, fatigue or diarrhea. The percentage of unsolicited AEs through Day 22 post-vaccination was 16% in both groups; 4% in Fluad versus 5% in Agriflu were considered by the investigator to be related. The percentages of subjects with a serious AE (SAE) during the 1 year trial were similar between vaccine groups (7% in each). Four SAEs were assessed to be possibly or probably related to the trial 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. No imbalances were noted with regard to Adverse Events of Special Interest (AESIs) or New Onset of Chronic Disease (NOCD). Overall, 26 (0.8%) Fluad recipients and 21 (0.6%) Agriflu recipients experienced an AESI. The most common AESI in both groups by system organ class was musculoskeletal/connective tissue/bone disorders (15 Fluad recipients and 7 Agriflu recipients) and endocrine disorders (all hypothyroidism; 4 Fluad recipients and 9 Agriflu recipients). Six percent of subjects in each group reported onset of a NOCD during the trial. The most commonly reported classes of NOCDs were vascular disorders (50 Fluad recipients and 51 Agriflu recipients), metabolism/nutrition disorders (44 and 33, respectively), musculoskeletal/connective tissue/bone disorders (38 and 27, respectively) and cardiac disorders (25 and 31, respectively). There were no deaths within 21 Days of vaccine administration. Deaths occurring during the 1 year trial duration were reported in similar proportions in both the Fluad and Agriflu groups: 1.5% and 1.3%, respectively and none were related to vaccine.

In the supportive studies, Fluad was associated with increased solicited local and systemic reactogenicity when compared to the unadjuvanted vaccine, but the majority of events were mild in severity. Also, the rates for moderate and severe AEs were balanced between groups. The duration of follow-up for unsolicited AEs ranged from 3 weeks to 6 months post-vaccination. Within 30 days of vaccination, the unsolicited AEs were balanced and uncommon. There were no imbalances noted either in overall deaths or in causes of death, in SAEs or in AESIs. In extension studies, re-vaccination did not show any increase in reactogenicity across treatment arms. However, bias might have been introduced in these trials by virtue of the fact that not all subjects returned for repeat dosing. In one of the revaccination studies, an imbalance in the number of deaths in the Fluad arm was noted. Causes of death included cardiovascular events, malignancy, trauma, gastrointestinal disorders, and respiratory failure. Clinical characteristics of the deaths, including the variable causes, timing since vaccination, and underlying medical conditions, did not provide evidence for a causal relationship with Fluad.

Regarding the post-marketing experience for Fluad, an estimated 75.7 million doses have been administered, and the most recent periodic safety report summarized the cumulative experience since post-marketing data collection began on May 15, 1997. No safety signals have emerged.

CBER reviewed and found Novartis' proposed pharmacovigilance plan (PVP), as described in EU Risk Management Plan version 3.0 acceptable. The Plan identifies potential (convulsion, neuritis, encephalitis, vasculitis, Guillain-Barré Syndrome (GBS), demyelination, Bell's palsy, immune thrombocytopenia (ITP), haemolytic anaemia, and vaccination failure) and identified (anaphylaxis and extensive limb swelling (ELS)) risks following Fluad vaccination for which it will continue to provide ongoing data. In addition, Novartis agreed to provide to the Vaccine Adverse Event Reporting System (VAERS) expedited 15-day reports for: neuritis, encephalomyelitis, vasculitis, Guillain-Barre Syndrome, demyelination, Bell's Palsy, and ITP. Novartis also agreed to provide summaries of AEs of Special Interest (AESIs) in the periodic (quarterly) reports, as required under 21 CFR§600.80(c)(2), using the same list of conditions as described in the section "AEs of Special Interest (AESIs)" on pages 33–34 of PSUR 37.

Of note, some modifications occurred to the original PVP during the review. Specifically, Novartis will not perform the active surveillance activities in Canada and Italy as described in version 2.0; instead, it will perform enhanced passive surveillance in Italy for the upcoming 2015/2016 influenza season, in accordance with the European Medicines Agency (EMA) "Interim Guidance on Enhanced Safety Surveillance for Seasonal Influenza Vaccines in the EU."

An additional active surveillance study will be conducted in the Lazio region in Italy; however, it is investigator-initiated, and Novartis is not the sponsor for this activity. CBER has requested Novartis to incorporate the details of the Lazio study into the Risk Management Plan. The Risk Management Plan version 3.0 is also undergoing review in Europe; after incorporating any additional requested changes by Reference Member State in Europe, Novartis will provide an updated Risk Management Plan version.

8. Advisory Committee Meeting

On September 15, 2015, CBER convened a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting to review and discuss presentations of safety and immunogenicity data derived from studies conducted with Fluad and submitted in the BLA. The committee voted affirmatively that the available data support the safety (10 yes, 2 no, 1 abstain) and effectiveness (11 yes, 1 no, 1 abstain) of Fluad and approval under the accelerated approval regulations for the proposed indication in adults aged 65 years of age and older [2].

9. Labeling

Novartis submitted revised versions of the PI as well as carton and container labels in response to comments provided by CBER during labeling negotiations. The revised PI and carton/container labels were reviewed by the Chair and members of the Review Committee (clinical, statistical, product, pharmacovigilance, and Advertising and Promotional Labeling Branch (APLB) reviewers), as appropriate.

Major changes recommended for product labeling included:

- Revising the proposed proper name: from "Fluad 65" to "Fluad."
- Removal of language on needle size needed for IM injection.
- Revising the language describing the tip caps of the pre-filled syringes: from "may contain natural rubber latex" to "contain natural rubber latex."
- Adding information on AESIs
- Adding information on the deaths observed in a revaccination trial.
- Removal of information obtained from secondary immunogenicity objectives.

Based on the conclusions drawn from a nonclinical reproductive and developmental toxicity study (see Section 4: *Nonclinical Pharmacology/Toxicology*), Fluad received a Pregnancy Category B designation and this is reflected in the PI under Section 8.1. *Pregnancy*.

Final versions of the PI, carton, and container labels were agreed upon through communications with Novartis. The Applicant will be advised to submit the final content of labeling in Structured Product Labeling (SPL) format after approval.

10. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

Based on the review of the clinical, pre-clinical, and product-related data submitted in the original BLA, the review committee recommends approval of Fluad for the proposed indication and usage.

Moreover, based on the previous discussions held between CBER and Novartis throughout the clinical development phase of Fluad; current policy stated in the Guidance for Industry "Clinical Data Needed to Support the Licensure of Seasonal Influenza Vaccines" [1]; and the combined manufacturing, pre-clinical, and clinical data submitted in the BLA, the Chair concurs with OVRR's decision to license Fluad via the accelerated approval pathway.

b) Risk/Benefit Assessment

In view of the data submitted to support the safety and effectiveness of Fluad that have been presented and discussed in this document, as well as the high degree of morbidity and mortality associated with seasonal influenza virus illness in adults aged 65 years and older, the review committee is in agreement that the benefit/risk profile for Fluad is favorable with respect to the intended indication and usage.

c) Recommendation for Postmarketing Risk Management Activities

There was no recommendation for postmarketing risk management activities. See below for the required and recommended postmarketing activities associated with the licensure of this product.

d) Recommendation for Postmarketing Activities

As discussed above, Novartis is required to conduct the following postmarketing activities:

1) Under the accelerated approval regulation (21 CFR § 601.41), the sponsor is required to study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit. Postmarketing trial(s) must also be adequate and well-controlled and should be conducted with due diligence [1].

2) In accordance with PREA under Section 505B(a) of the Food Drug and Cosmetic Act (FDCA), pediatric trials are required.

The postmarketing activities which Novartis has committed to and are to be included in the approval letter are shown below:

POSTMARKETING STUDIES SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR § 601.70

EFFICACY REQUIREMENTS

1. Confirmatory absolute efficacy trial of Fluad aQIV (V118_18) comparing an MF59 adjuvanted quadrivalent inactivated seasonal influenza vaccine (Fluad aQIV) with an active control Tdap vaccine (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed [Boostrix]) in adults $\geq$ 65 years of age.

   Final Protocol Submission: September 2015
   Study Completion Date: November 2018

Final Report Submission: August 2019

PEDIATRIC REQUIREMENTS

1. Deferred pediatric trial V118_05 under PREA to evaluate the efficacy, safety and immunogenicity of Fluad (aQIV) when administered to children 6 to < 72 months of age.

   Study Completion Date: July 2018
   Final Report Submission: April 2019

2. Deferred pediatric trial V70_29 under PREA to evaluate the safety and immunogenicity of Fluad when administered to children 6 to < 72 months of age.

   Final Report Submission: April 2019

3. Deferred pediatric trial V118_19 under PREA to evaluate the safety and immunogenicity of Fluad (aQIV) when administered to children 6 to < 9 years of age.

   Final Protocol Submission: September 2020
   Study Completion Date: May 2022
   Final Report Submission: February 2023

4. Deferred pediatric trial V118_14 under PREA to evaluate the safety and immunogenicity of Fluad (aQIV) when administered to infants < 6 months of age.

   Final Protocol Submission: September 2020
   Study Completion Date: May 2022
   Final Report Submission: February 2023

11. References

1. Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines, 2007. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074794.htm.
2. Vaccines and Related Biological Products Advisory Committee Meeting (September 15, 2015). Transcript available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM466047.pdf.