Application Type	BLA
STN	103914/5726
CBER Received Date	December 30, 2013
PDUFA Goal Date	November 1, 2014
Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name(s)	Roshan Ramanathan MD, MPH
Review Completion Date / Stamped Date	October 29, 2014
Supervisory Concurrence	Jeffrey Roberts MD
Applicant	Sanofi Pasteur Inc.
Established Name	Influenza Virus Vaccine
(Proposed) Trade Name	Fluzone High-Dose
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Trivalent, split virion, inactivated influenza virus vaccine
Dosage Form(s) and Route(s) of Administration	Suspension for injection available in 0.5 mL single-dose, prefilled syringe to be administered by intramuscular injection
Dosing Regimen	A single 0.5 mL dose for intramuscular injection in adults 65 years of age and older
Indication	Fluzone High-Dose is indicated for active immunization against influenza disease caused by influenza subtype A viruses and type B virus contained in the vaccine.
Orphan Designated	No

Table of Contents

Glossary

ACIP Advisory Committee on Immunization Practices

AE adverse event

BLA biologics license application
CDC Centers for Disease Control
CI confidence interval
CFR Code of Federal Regulation
CMC chemistry, manufacturing, and controls
CRF case report form
eCTD electronic Common Technical Document
EMA European Medicines Agency
ELISA Enzyme-Linked Immunosorbent Assay
ES Executive Summary
FDAAA Food and Drug Administration Amendments Act of 2007
GBS Guillain-Barré Syndrome
GMR geometric mean ratio
GMT geometric mean titer
GRMP good review management principles
HA hemagglutinin antigen
HAI hemagglutinin inhibition assay
HI hemagglutinin inhibition
ICF informed consent form
ILI influenza-like illness
IND investigational new drug application
LB lower bound
NCT National Clinical Trials
PI package insert
pIMD potential immune-mediated disease
PMC postmarketing commitment
PMR postmarketing requirement
PREA Pediatric Research Equity Act
b(4)-PCR ----b(4)---------- polymerase chain reaction
SAE serious adverse event
sBLA supplement to a Biologics License Application
TIV trivalent influenza vaccine
VE vaccine efficacy

1. Executive Summary

Fluzone High-Dose is a trivalent, split-virion, inactivated, seasonal influenza virus vaccine containing 60 mcg hemagglutinin (HA) antigen per virus strain (for a total of 180 mcg HA antigen per dose). Fluzone High-Dose was licensed in the United States under the accelerated approval regulations (21 CFR 601.41), based on demonstration of an effect on a surrogate endpoint (hemagglutination inhibition assay geometric mean titer or HAI GMT) likely to predict clinical benefit. Fluzone High-Dose is indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B virus contained in this vaccine. Fluzone High-Dose is approved for use in persons 65 years of age and older.

With this supplement to the Biologics License Application (sBLA) for Fluzone High-Dose, Sanofi Pasteur Inc. addresses the requirement to conduct a post-approval study to verify and describe the anticipated clinical benefit of Fluzone High-Dose, which was licensed under the accelerated approval regulations in 2009. The single clinical study submitted in this supplement, FIM12, is a randomized, modified double-blind, clinical endpoint efficacy study compares standard dose Fluzone to Fluzone High-Dose and was conducted in adults 65 years of age and older. Participants were randomized 1:1 to receive either Fluzone High-Dose or Fluzone. The study was conducted over two influenza seasons (2011-2012 and 2012-2013); subjects enrolled in the first year of the study were allowed to be re-enrolled and re-randomized in the second year. The per-protocol analysis set for efficacy assessments included 15,892 Fluzone High-Dose recipients and 15,911 Fluzone recipients. The primary endpoint of the study was the occurrence of laboratory-confirmed influenza (as determined by culture or polymerase chain reaction) caused by any influenza viral type/subtype in association with protocol-defined influenza-like illness (ILI), defined as the occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrent with at least one of the following systemic symptoms: temperature >99.0°F, chills, tiredness, headaches or myalgia. Participants were monitored for ILI by both active and passive surveillance, starting 2 weeks post-vaccination for approximately 7 months. After an episode of ILI, nose and throat swab samples were collected for analysis; attack rates and relative vaccine efficacy (VE) were calculated. The efficacy of Fluzone High-Dose relative to Fluzone against laboratory-confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) was 24.24% (95% confidence interval (CI): 9.69; 36.52). The study met the pre-specified criterion for demonstration of superiority of Fluzone High-Dose over Fluzone (lower bound of the 95% CI was >9.1%). A pre-specified secondary endpoint of the study was the occurrence of culture-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations in association with a modified CDC-defined ILI, defined as the occurrence of a temperature > 99.0°F (> 37.2°C) with cough or sore throat. The efficacy of Fluzone High-Dose relative to Fluzone for this endpoint was 51.1% (95% CI: 16.8; 72.0).

With respect to safety, FIM12 did not demonstrate an increase in the rates of deaths, serious adverse events (SAEs), and adverse events of special interest (AESIs) associated with vaccination with Fluzone High-Dose compared to Fluzone. Of note, differences in the rates of solicited local and systemic adverse reactions within one week post-vaccination with Fluzone High-Dose and Fluzone were not evaluated in study FIM12. Solicited local and systemic adverse reactions were evaluated in a clinical study

pre-licensure. In this study, adults 65 years of age and older randomized to receive either Fluzone High-Dose (n=2573) or Fluzone (n=1260) reported an increase in local and systemic reactogenicity in association with Fluzone High-Dose compared to Fluzone, that was generally mild and self-limited. As the risks of vaccination with Fluzone High-Dose 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 influenza types/subtypes contained in the vaccine, the overall risk-benefit profile of Fluzone High-Dose has been determined to be favorable.

This supplement does not trigger the Pediatric Research Equity Act because it does not contain information pertaining to a new active ingredient, new indication, new dosage form new dosing regimen or new route of administration. At the time of initial licensure of Fluzone High-Dose, the pediatric study requirement was waived for ages 0 to 6 months because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group, and is not likely to be used.

No changes to the existing pharmacovigilance plan for Fluzone High-Dose are recommended based on the information contained in this supplement.

In conclusion, the data submitted by the applicant in this sBLA support the traditional approval of Fluzone High-Dose for the active immunization of persons 65 years of age and older against influenza disease caused by virus subtypes A and type B contained in the vaccine. Approval of this supplement fulfills the requirement communicated in the December 23, 2009 approval letter to Sanofi Pasteur, Inc. to conduct an active-controlled clinical endpoint efficacy study that verifies the clinical benefit of Fluzone High-Dose in adults 65 years of age and older.

2. Clinical and Regulatory Background

Fluzone High-Dose was licensed on December 23, 2009 for the active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. Clinical evaluation of Fluzone High-Dose included a Phase 3 study, FIM05, that evaluated lot-to-lot consistency of manufacturing of Fluzone High-Dose and compared post-vaccination hemagglutination inhibition (HI) antibody titers between Fluzone High-Dose and standard Fluzone in individuals 65 years of age and older. The study was designed to demonstrate an effect on a surrogate endpoint (HI) that is reasonably likely to predict clinical benefit, providing the basis of effectiveness to support accelerated approval of Fluzone High-Dose. Per 21CFR601 Subpart E, the Applicant must confirm the clinical benefit of the product. For this reason, at the time of approval of Fluzone High-Dose, Sanofi Pasteur Inc. agreed to submit the results of study FIM07, an active-controlled clinical endpoint efficacy and safety study of Fluzone High-Dose compared to standard dose Fluzone in 27,000-30,000 adults 65 years of age and older as the confirmatory study. However, during the first year of study FIM07 (2009-2010), 22 laboratory-confirmed cases of influenza were identified, or which 21 were classified as novel H1N1 by genomic sequence. No cases of influenza caused by strains similar to the vaccine components (primary endpoint) were identified. For this reason, on May 31, 2011, CBER agreed that FIM07 could be terminated, and that Sanofi Pasteur Inc. could conduct the required confirmatory efficacy trial under a different trial protocol, FIM 12. Sanofi Pasteur Inc. submitted draft protocols for FIM12 “Efficacy Study of Fluzone High-Dose Vaccine compared with Fluzone Vaccine in Elderly Adults” and on November 22, 2011, CBER agreed to issue a release

for the post-marketing requirement to conduct study FIM07 and agreed to a new timeline for FIM12.

At the time of initial licensure of Fluzone High-Dose (December 23, 2009), the pediatric study requirement was waived for ages 0 to 6 months because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this age group. Fluzone High-Dose (60 µg HA/strain/0.5 mL) is intended for adults 65 years of age and older because immune responses to inactivated influenza vaccines at the standard dose of 15 µg HA/strain/0.5 mL are lower than those in younger adults. Standard dose Fluzone is appropriately labeled for use in ages 6 months to 18 years for this indication. Therefore, no additional studies were deemed to be needed in the pediatric population, and a full waiver was granted for all pediatric age groups.

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, 3). Influenza causes morbidity in all ages, with the highest rates of serious morbidity and death among older adults and persons with specific underlying medical conditions, such as chronic pulmonary or cardiac disease (4, 5). 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 (4,5). Adults ≥ 65 years of age also account for the majority (90%) of deaths from seasonal influenza in the United States (4,5).

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

Currently, 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 (6).

2.3 Safety and Efficacy of Pharmacologically Related Products

Inactivated whole-virus influenza vaccines have been commercially available since the 1940s. 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. Currently, six inactivated trivalent standard dose influenza vaccines are licensed in the U.S for use in adults 65 years of age and older. These include Fluzone®, Flucelvax®, Fluvirin®, FluLaval®, Fluarix®, and Afluria®. In addition, 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®. 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.
Although 6 licensed, standard dose, inactivated influenza vaccines currently are available to adults 65 years of age and older, immune responses to yearly influenza vaccination is substantially lower in this population, possibly due to decreased T-cell-dependent antibody responses, comorbidities, and functional disabilities observed in this population (7).

Prior to the submission of this efficacy supplement, no clinical studies had verified efficacy of Fluzone High-Dose in the prevention of laboratory-confirmed ILI in adults 65 years of age and older. Prior to the initial licensure of Fluzone High-Dose via accelerated approval, a multi-center, double-blind trial conducted in the US evaluated the immunogenicity of Fluzone High-Dose (n=2576) compared to Fluzone (n=1275) in adults 65 years of age and older. The study met pre-defined criteria for demonstration of superiority of Fluzone High-Dose compared to Fluzone with respect to 28 day post-vaccination HAI GMTs (lower limit of the 95% CI of the GMT ratio >1.5) and seroconversion rates (lower limit of 95% CI of the difference of the seroconversion rates >10%) for two influenza A strains contained in the vaccine: (H1N1) and A(H3N2). The pre-specified criteria for superiority were not met with respect to Influenza B. For the influenza strain B, however, non-inferiority of Fluzone High-Dose compared to Fluzone was demonstrated based on HAI GMTs and seroconversion rates (8).

Prior to the initial licensure of Fluzone High-Dose in 2009, the safety of Fluzone-High-Dose was previously evaluated in a multi-center, double-blind trial conducted in the US comprising of 2573 Fluzone High-Dose recipients and 1260 Fluzone recipients. Solicited injection-site reactions and systemic adverse reactions were more frequent after vaccination with Fluzone High-Dose compared to Fluzone. The most frequent adverse reactions (occurring in ≥ 10% of persons vaccinated) associated within 7 days of use of Fluzone High-Dose in adults 65 years of age and older are: injection-site pain, injection-site erythema, myalgia, malaise and headache. Onset of symptoms was within the first 3 days after vaccination and the majority of the reactions resolved within 3 days. Less than 1.9% of these adverse reactions were severe. No differences in serious adverse events or deaths have been associated with use of Fluzone High-Dose when compared to Fluzone.

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 (9). Anaphylaxis and other allergic/hypersensitivity reactions (including Stevens-Johnson syndrome, urticarial and angioedema) have been described in association with the use of Fluzone or Fluzone High-Dose. No clinically meaningful differences between Fluzone and Fluzone High-Dose in the rates of these less common AEs was apparent in the clinical data.

In the opinion of the clinical reviewer who reviewed Fluzone High-Dose at the time of its initial approval, the adverse event profile of Fluzone High-Dose compared to standard dose Fluzone in older adults does not outweigh the potential for clinical benefit as demonstrated in the evaluation of a surrogate marker for efficacy in study FIM 05 (10).

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

Fluzone High-Dose was licensed on December 23, 2009. As of the most recent Development Safety Update Report for Fluzone High-Dose submitted by Sanofi Pasteur Inc., submitted on June 23, 2014, an estimated 25,090 subjects have received Fluzone High-Dose vaccine in clinical studies since the 2006-2007 influenza seasons. Since the 2006-2007 influenza season, a total of –b(4)------ doses of Fluzone High-Dose have been distributed worldwide. There has been no increase in reporting frequency or event severity of any identified or potential risks associated with Fluzone vaccines, including Fluzone High-Dose. Therefore, the benefit-risk balance remains unchanged based on the collective post-marketing experience to date.

The Office of Biostatics and Epidemiology (OBE), CBER conducted a post-licensure safety surveillance assessment of Fluzone High-Dose using the Vaccine Adverse Event Reporting System (VAERS) during the time period from July 1, 2010 through December 31, 2010 (11). Consistent with pre-licensure experience, fever, pain and headache were among the most frequent adverse events reported after receipt of Fluzone High-Dose. Using evidence based data mining methods, an imbalance between the reported and expected number of gastrointestinal events (vomiting) was observed. There was no disproportionate reporting of cases of anaphylaxis or GBS. Of note, due to the limitations of passive surveillance, VAERS findings need to be interpreted with caution due to biased reporting, inconsistency in quality and completeness of reports and issues related to over reporting or underreporting. VAERS reporting can, however, detect imbalances that can be further studied in the context of a randomized clinical study (such as FIM12, the randomized trial submitted to this efficacy supplement). For further discussion of the safety evaluation of Fluzone High-Dose in FIM12 pertaining to this reported imbalance, please see Section 6.1.11.4.

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

Pre-submission interactions with the applicant that represent important milestones in the establishment and conduct of the clinical development program are briefly summarized below.

CBER did not concur with Sanofi Pasteur Inc.'s proposed definition of influenza-like illness (ILI) to refer to respiratory illness in the absence of any systemic symptoms as the clinical symptom criterion for case determination because of reduced specificity and the potential for counting clinically irrelevant illnesses as cases of influenza. Sanofi Pasteur indicated that using the respiratory illness definition (without systemic symptoms) as a primary definition would increase the cases by about 60%, representing an advantage. CBER recommended that case determination be based on an ILI definition that includes both respiratory and systemic symptoms. In the final FIM12 clinical study protocol, the definition of ILI included systemic symptoms (see Section 6.1.6).

On August 25, 2011, CBER communicated to Sanofi Pasteur Inc. a preference for the clinical endpoint demonstrating relative vaccine efficacy against culture confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the vaccine, associated with CDC-defined ILI. In the final FIM12 clinical study protocol, the primary endpoint in the study was "to compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults with respect to laboratory-confirmed influenza caused by any influenza viral types/subtypes associated with the occurrence of protocol-defined

ILI." Please see Section 6.1.7 of this review for additional information. CBER also communicated to Sanofi Pasteur Inc., that efficacy endpoints based on case definitions of ILI defined as "respiratory illness" will not be considered high priority in support of the primary endpoint.

CBER did not concur with Sanofi's proposal to shorten the length of surveillance for case ascertainment. CBER viewed it important to continue case ascertainment if public health surveillance shows more than sporadic influenza activity in the study areas or if cases of influenza were still being identified among study participants. In the final FIM12 clinical study protocol, the active surveillance period was extended per CBER's recommendation (see Table 2).

CBER recommended that that FIM12 subjects who participated in a prior year not be re-enrolled and re-randomized in the subsequent year in order to avoid confounding effects of the previous year's vaccination on the efficacy of Fluzone High-Dose or Fluzone in the subsequent year. Sanofi Pasteur responded that CBER's recommendation would not be feasible because of operational limitations regarding the available pool of eligible participants and because of difficulties determining what influenza vaccine was received. In the final FIM12 clinical study protocol (see Section 6.1.5), subjects who participated in a prior year were allowed to re-enroll and re-randomize the subsequent year because: 1) re-enrolling and re-randomizing Year 1 subjects would produce a more conservative estimate of relative efficacy (lower relative efficacy) 2) the applicant provided simulation results showing that re-enrollment would not overestimate relative VE.

CBER recommended that the lower bound of the 95% confidence interval for demonstration of superiority should be close to 10% consistent with CBER's current vaccine recommendations to all vaccine manufacturers requesting a superiority claim. A lower bound of the 95% confidence interval significantly lower than 10% High-Dose would substantially increase the uncertainty about whether Fluzone High-Dose provides clinically meaningful benefit over Fluzone. CBER accepted a lower bound of 95% CI for relative VE to be at least 9.1% because the design of FIM12 permitted re-enrollment of Year 1 subjects; therefore, it was anticipated that the study would provide a conservative estimate of relative efficacy (lower relative efficacy). Hence, acceptance of this criterion appeared reasonable.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

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

3.2 Compliance With Good Clinical Practices And Submission Integrity

According to the applicant, the trial was performed in compliance with Good Clinical Practice (GCP). No reviewer on the FDA review committee, including this clinical reviewer, identified any issues with respect to data integrity.

3.3 Financial Disclosures

The applicant certified that no financial arrangements with any clinical investigators exist where the value of compensation to the investigator could be affected by the outcome of the study as defined in 21CFR54.2(a)(b) and (f). There were also no significant payments ($25,000 or more) to any clinical investigator, and no investigator had a $50,000 or more equity interest in the study vaccine [as required in 21 CFR 54.4 (a) (3) (iii-iv), 54.2(b-c)].

Covered clinical study (name and/or number): Study FIM12: Phase IIIb/IV Efficacy Study of Fluzone High-Dose Vaccine Compared with Fluzone Vaccine in Elderly Adults		
Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 456		
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		
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		

Reviewer Comment: The financial disclosures do not raise any concerns with respect to the integrity of the study.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

The chemistry, manufacturing and controls for Fluzone High-Dose were not modified or addressed in this submission. Therefore, this supplement did not include Modules 2, 3 or 4 (CMC) information. For verification, please refer to the review by Dr. Vladimir Lugovtsev, Division of Viral Products/OVRR/CBER.

4.2 Assay Validation

The following assays used in study FIM12 were found to be validated and suitable for intended use by Drs. Vladimir Lugotsev OVRR/Division of Viral Products and Tielin Qin, OBE/Division of Biostatistics/Vaccine Evaluation Branch:

1) hemagglutinin inhibition (HI) assay
2) procedures for the ---b(4)---------- nasopharyngeal (NP) swabs
3) methods used for antigenic typing by culture
4) real-time ----------b(4)---------- polymerase chain reaction (b(4)PCR) for identification of influenza viruses
5) identification of respiratory viruses by using -----b(4)----------
6) ----------b(4)----------

Please see Dr. Lugotsev's review and Dr. Qin's review for additional details.

4.3 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.

Reviewer Comment: When there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome, accelerated approval of a vaccine is subject to the requirement that the applicant study the vaccine further, to verify and describe its clinical benefit. Fluzone High-Dose was approved via accelerated approval in 2009 and the applicant was required to conduct FIM12 study to verify clinical benefit per 21CFR314.500.

4.4 Statistical

The statistical reviewer verified that the study endpoint analyses and subgroup analyses of efficacy and safety cited by the Applicant were supported by the submitted data.

Please see review by Dr. Sang Ahnn, OBE/Division of Biostatistics/Vaccine Evaluation Branch for details

4.5 Pharmacovigilance

No potential safety concerns were identified by this clinical reviewer of this supplement to warrant a revision to the existing pharmacovigilance plan for Fluzone High-Dose.

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

5.1 Review Strategy

A single Phase 3 study, for both efficacy and safety (FIM12), was submitted to this supplement and reviewed in depth in Section 6. Earlier phase studies did not materially impact the analysis or the conclusions of the review. The review strategy for FIM12 was to focus on both primary and secondary endpoints related to the use of modified-CDC defined ILI and protocol-defined ILI, but not on respiratory illness, as definition for ILI, due to the lack of specificity of this definition for influenza disease. (Please see Section 6.1.6 for definitions of these terms.) Post-hoc and exploratory analyses were reviewed but given minor importance as these endpoints did not impact labeling of Fluzone High-Dose.

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

The Clinical Study Reports (CSRs), pertinent case report tabulations and forms (module 5), labeling (module 1), financial information (module 1) were reviewed. In addition, amendments to the supplement (5726.5000, 5726.5001, 5726.5002, 5726.5003, 5726.5004, and 5726.5005) were also reviewed.

5.3 Table of Studies/Clinical Trials

The table below summarizes the clinical study submitted to this supplement for review.

Table 1. Summary of Studies Submitted to BLA 103914/5726

Study	Design	Control	Total # Subjects	Age (Years)	Countries
FIM12	Randomized, modified double-blind*, multi-center study	Fluzone	31,989 (15,991 in the Fluzone High-Dose Group and 15,998 in the Fluzone group)	65 years of age and older	United States and Canada

*Modified double-blind meant that the unblinded qualified study member, independent of the safety evaluation and other trial 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.

The duration of follow up for each subject was 6 to 8 months, depending on time of enrollment. Subjects were randomized 1:1 to either Fluzone or Fluzone High-Dose.

5.4 Literature Reviewed

1. World Health Organization. (2009) Influenza (Seasonal). WHO Fact Sheet No. 211. accessed at: www.who.int/mediacentre/factsheets/fs211/en

2. MG Thompson, PhD, DK Shay, MD, H Zhou, MSc, MPH, CB Bridges, MD, PY Cheng, PhD, E Burns, MA, JS Bresee, MD, NJ Cox, PhD, Influenza Div, National Center for Immunization and Respiratory Diseases, CDC. Estimate of Deaths Associated with Seasonal Influenza- United States, 1976-2007. MMWR August 27, 2010; 59(33);1057-1062. Retrieved from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5933a1.htm

3. Centers for Disease Control and Prevention (CDC). Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. Morb Mortal Wkly Rep. 2010 Aug 27;59(33):1057-62.

4. Epperson S, Blanton L, Kniss K, Mustaquim D, Steffens C, Wallis T, Dhara R, Leon M, Perez A, Chaves S, Abd Elall A, Gubareva L, Xu Xiyan, Villaneuva J, Bresse J, Cox N, Finelli L, Brammer L. Influenza Activity – United States, 2013-14 Season and Composition of the 2014-15 Influenza Vaccines. MMWR June 6, 2014, 63(22); 483-490. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6322a2.htm

5. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, Fukuda K. Influenza-associated hospitalizations in the United States. JAMA. 2004 Sep 15;292(11):1333-40.

6. Centers for Disease Control and Prevention (CDC). Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Report. 2011 January 21; 60 (1): 1-28.

7. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. Ann Intern Med. 1995;123:518-27

8. Fluzone High-Dose® [Package Insert]. Sanofi Pasteur Inc., Swiftwater, PA; June 2014. Accessed September 17, 2014. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM305079.pdf.

9. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré Syndrome and the 199201993 and 1993-1994 influenza vaccines. N Engl J Medicine 1998; 339:1797-180.

10. Cvetkovich, Therese. Clinical Review, Fluzone High-Dose STN103914/5240, December 8, 2009.

11. Moro P, Arana J, Cano M, Menschik D, Yue X, Lewis P, Haber P, Martin D, Broder K. Postlicensure Safety Surveillance for High-Dose Trivalent Inactivated Influenza Vaccine in the Vaccine Adverse Event Reporting System, 1 July 2010-31 December 2010. Clinical Infectious Diseases 2012;54(11):1608-1614.

12. Hobson D, Curry RL, Beare AS, Ward- Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J. Hyg. (Lond.)* 70(4),767–777 (1972).

13. Reber A, Immunological assessment of influenza vaccines and immune correlates of protection. Expert Rev Vaccines 12 (5):519-536 (2013).

14. Ohmit SE, Petrie JG, Cross RT, Johnson E, Monto AS. Influenza hemagglutination inhibition antibody titer as a correlate of vaccine-induced protection. *J. Infect. Dis.* 204(12), 1879–1885 (2011).

15. Boivin G, Hardy I, Tellier G, Maziade J. Predicting Influenza Infections During Epidemics with Use of a Clinical Case Definition. Clin Infect Diseases 200 Nov; 31 (5): 1166-9.

16. Navarro-Mari JM, Perez-Ruiz M, Cantudo-Munoz P, Petit-Gancedo C, Jimenez Valera M, Rosa-Fraile M. Influenza-like-illness criteria were poorly related to laboratory-confirmed influenza in a sentinel surveillance study. J Clin Epidemiol 2005 Mar; 58(3):275-9.

17. Fritz, Timothy. Summary Basis for Regulatory Action: Flublok. January 26, 2013. Retrieved from:

http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM338898.pdf.

18. FluMist® Quadrivalent [Package Insert]. MedImmune, LLC, Gaithersburg, MD; July 2014. Accessed September 17, 2014. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm294307.pdf

19. Klein S and Pekosz A. Sex-based Biology and the Rational Design of Influenza Vaccination Strategies. Journal of Infectious Diseases 2014;209(S3):S114-9.

20. Shoamanesh A., Traboulsee A. Acute disseminated encephalomyelitis following influenza vaccination. Vaccine 29 (2011) 8182-8185.

21. Menge T, Kieseier BC, Nessler S, Hemmer B, Hartun HP, Stuve O. Acute Disseminated Encephalomyelitis: an acute hit against the brain. Curr Opinion on Neurology 2007, 20:247-254.

22. Richards BW, Jones FD, Younge BR. Causes and prognosis in 4,278 cases of paralysis of oculomotor, trochlear and abducens cranial nerves. Am J Ophthalmol., 1992, 113: 489-496.

23. Gilden DH. Bell's Palsy. New England Journal of Medicine 351; 13. September 23, 2004.

6. Discussion of Individual Studies/Clinical Trials

6.1 Efficacy Study of Fluzone High-Dose Vaccine Compared with Fluzone Vaccine in Elderly Adults

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective of the study was to compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults with respect to laboratory-confirmed influenza caused by any influenza viral types/subtypes associated with the occurrence of protocol-defined influenza-like illness (ILI).

The secondary efficacy objectives considered key to this review are listed below:

1) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to culture-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a protocol-defined ILI
2) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to culture-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a modified Centers for Disease Control and Prevention (CDC)-defined ILI
3) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to laboratory-confirmed influenza caused by viral types/subtypes similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a protocol-defined ILI

4) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to laboratory-confirmed influenza caused by viral types/subtypes similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a modified CDC-defined ILI
5) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults with respect to laboratory-confirmed influenza caused by any viral types/subtypes associated with the occurrence of protocol-defined ILI
6) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to laboratory-confirmed influenza caused by any influenza viral types/subtypes, associated with the occurrence of a modified CDC-defined ILI

The evaluation of safety was an observational objective. The safety objectives were:
1) To describe the rates in each vaccine group of all serious adverse events (SAEs) (including adverse events of special interest [AESIs]) that occurred during the surveillance period)
2) To describe the rates in each vaccine group of all deaths that occurred during the surveillance

Exploratory objectives were:
1) To estimate an HAI correlate of protection against culture-confirmed influenza associated with protocol-defined ILI caused by each viral type/subtype antigenically similar to those contained in the vaccine formulations.
2) To estimate an HAI correlate of protection against laboratory confirmed influenza associated with protocol-defined ILI caused by each viral type/subtype similar to those contained in the vaccine formulations.

6.1.2 Design Overview

This was a Phase IIIb/IV randomized, modified double-blind, active-controlled, multi-center trial in elderly adults (≥65 years of age). The trial compared the efficacy of Fluzone High-Dose to that of Fluzone in preventing laboratory-confirmed (culture or polymerase chain reaction [PCR] influenza illness in elderly adults.

The trial period was from September 6, 2011 to May 31, 2013. The study was completed after 2 influenza seasons.

6.1.3 Population

Inclusion Criteria:
A potential subject had to meet all of the following criteria to be considered for trial enrollment:
1) Aged ≥ 65 years on the day of vaccination
2) ICF signed and dated
3) Able to attend all scheduled visits and to comply with all trial procedures

Exclusion Criteria:
A potential subject meeting any of the following criteria was ineligible for trial enrollment:
1) Participation at the time of study enrollment (or in the 4 weeks preceding the trial vaccination), or planned participation during each year of the trial period, in another clinical trial investigating a vaccine, drug, medical device, or medical procedure

Note: Concomitant participation in an observational trial was acceptable
2) Vaccination against influenza in the 6 months preceding the trial vaccination
3) Systemic hypersensitivity to eggs, chicken proteins, or any of the vaccine components, or a history of a life-threatening reaction to Fluzone High-Dose or Fluzone vaccine or to a vaccine containing any of the same substances.
4) Personal history of GBS
5) Dementia or any other cognitive condition at a stage that could interfere with following the trial procedures
6) Thrombocytopenia contraindicating IM vaccination, as judged by the investigator
7) Bleeding disorder or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination, as judged by the investigator
8) Current alcohol abuse or drug addiction
9) Subject deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
10) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study
11) Moderate or severe acute illness with or without fever (oral temperature > 99.0°F [> 37.2°C]). If this contraindication existed, vaccination was to be deferred until the individual had been medically stable and/or afebrile (temperature ≤ 99.0 ºF [≤ 37.2°C]) for at least 24 hours.
12) Signs and symptoms of an acute infectious respiratory illness. If this existed, vaccination was to be deferred until the symptoms resolved.

Reviewer Comment: Clinical trials do not always precisely predict the observed efficacy of the product when used in common clinical practice, due to the characteristics of the population recruited for clinical trials (for example, exclusion of subjects with dementia, and subjects with current drug or alcohol abuse). However, the eligibility criteria for FIM12 did not exclude subjects with immunocompromising conditions and comorbidities. In this manner, the study population may be generally more representative of a 'real world' population. [Of note, information on concomitant immunosuppressive therapies was collected at the time of enrollment. For a subgroup analysis of safety and efficacy of Fluzone High-Dose relative to Fluzone in subjects with immunocompromised conditions, please see Section 9.1.3.]

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects received a single intramuscular injection of one of two U.S. licensed TIVs: Fluzone High-Dose or Fluzone. Either Fluzone High-Dose or Fluzone was administered by intramuscular injection into the left or right deltoid muscle (a 22-gauge 1-inch needle was recommended). Product formulation and lot numbers are provided below.

1) Fluzone High-Dose 60 mcg/HA (180 mcg total)

   Each 0.5 mL dose of vaccine contained the following 3 influenza virus strains:
   Year 1: Fluzone High-Dose (Influenza Virus Vaccine, 2011-2012 strains)
   A/California/7/2009 (H1N1) 60 mcg
   A/Victoria/210/2009 (H3N2) 60 mcg
   B/Brisbane/60/2008 (B/Victoria lineage) 60 mcg

The batch/lot numbers selected for Year 1 (2011) were UD15256 (US) and UD15257 (Canada) for Fluzone High-Dose.

Year 2: Fluzone High-Dose (Influenza Virus Vaccine, 2012-2013 strains)
A/California/7/2009 (H1N1) 60 mcg
A/Victoria/361/2011 (H3N2) 60 mcg
B/Texas/6/2011 (a B/Wisconsin/1/2010 like virus/B/Yamagata lineage) 60 mcg

The batch/lot numbers selected for Year 2 (2012-2013) of the trial were UD15896 (US) and UD15895 (Canada) for Fluzone High-Dose.

2) Fluzone 15 mcg/HA (45 mcg total)

Each 0.5 mL dose of vaccine contained the following 3 influenza virus strains:
Year 1: Fluzone High-Dose (Influenza Virus Vaccine, 2011-2012 strains)
A/California/7/2009 (H1N1)15 mcg
A/Victoria/210/2009 (H3N2) 15 mcg
B/Brisbane/60/2008 (B/Victoria lineage) 15 mcg

The batch/lot numbers selected for Year 1 (2011) were UD15222 (US) and US15225 (Canada) for Fluzone.

Year 2: Fluzone High-Dose (Influenza Virus Vaccine, 2012-2013 strains)
A/California/7/2009 (H1N1) 15 mcg
A/Victoria/361/2011 (H3N2)15 mcg
B/Texas/6/2011 (a B/Wisconsin/1/2010 like virus/B/Yamagata lineage) 15 mcg

The batch/lot numbers selected for Year 2 (2012-2013) of the trial were UD 15893 (US) and UD15894 (Canada) for Fluzone.

6.1.5 Sites and Centers

The trial was conducted in 126 sites in the United States and Canada. 99 sites participated during Year 1 and 119 sites participated during Year 2. 92 sites participated in both Years 1 and 2.

Reviewer Comment: Since the study had to be conducted over two influenza seasons, and the influenza virus strains contained in the vaccines varies each year, the trial evaluates the efficacy of two different formulations of Fluzone or Fluzone High-Dose as described in Section 6.1.4. Please see Section 2.5 for a discussion on the decision to re-enroll subjects from Year 1 of the study.

6.1.6 Surveillance/Monitoring

The surveillance/monitoring plans for both safety and efficacy are summarized in the following tables.

Table 2. Table of Study Procedures

Visit/Contact Number	Visit 1	Visit 2	Final Telephone Call
Trial Timelines (Days)	Day 0	Day 28 (+7 days)	End of Study Year† (+7 days)
Informed Consent	X		
Inclusion and Exclusion Criteria	X		
Collection of demographic information	X		
Collection of reportable history	X		
Collection of vaccination history‡	X		
Physical Examination	X		
Randomization	X		
Vaccination	X		
Immediate surveillance (20 min)	X		
Provision of memory aid§	X		
Blood draw (10 mL)*		X	
Collection of reportable vaccinations	At any time during the study period	At any time during the study period	At any time during the study period
Collection of reportable medications	At any time during the study period	At any time during the study period	At any time during the study period
Collection of respiratory illness symptoms through passive and active surveillance	Passive surveillance: Subjects were instructed to contact the study site if they experienced symptoms of respiratory illness from Day 14 post-vaccination until April 30 the following year. Active surveillance: Between Day 14 after vaccination and approximately 31 December and between approximately 01 March and 30 April the call center contacted subjects once a week. Between approximately Jan 1 and end of February of the influenza season, the call center contacted subjects twice a week.	Passive surveillance: Subjects were instructed to contact the study site if they experienced symptoms of respiratory illness from Day 14 post-vaccination until April 30 the following year. Active surveillance: Between Day 14 after vaccination and approximately 31 December and between approximately 01 March and 30 April the call center contacted subjects once a week. Between approximately Jan 1 and end of February of the influenza season, the call center contacted subjects twice a week.	Passive surveillance: Subjects were instructed to contact the study site if they experienced symptoms of respiratory illness from Day 14 post-vaccination until April 30 the following year. Active surveillance: Between Day 14 after vaccination and approximately 31 December and between approximately 01 March and 30 April the call center contacted subjects once a week. Between approximately Jan 1 and end of February of the influenza season, the call center contacted subjects twice a week.
Collection of NP swabs for laboratory confirmation of influenza**	From Day 14 post-vaccination until April 30 of the following year, every effort had to be made to obtain NP specimen on the same or following day after confirmation of qualifying symptoms and no later than 5 days after onset of respiratory illness.	From Day 14 post-vaccination until April 30 of the following year, every effort had to be made to obtain NP specimen on the same or following day after confirmation of qualifying symptoms and no later than 5 days after onset of respiratory illness.	From Day 14 post-vaccination until April 30 of the following year, every effort had to be made to obtain NP specimen on the same or following day after confirmation of qualifying symptoms and no later than 5 days after onset of respiratory illness.

Visit/Contact Number	Visit 1	Visit 2	Final Telephone Call
Collection of disease burden and health care in formation	At any time during the study year in association with a respiratory illness and for 30 days (+7 days) following the start of a qualifying symptom regardless of whether or not an NP swab was obtained.	At any time during the study year in association with a respiratory illness and for 30 days (+7 days) following the start of a qualifying symptom regardless of whether or not an NP swab was obtained.	At any time during the study year in association with a respiratory illness and for 30 days (+7 days) following the start of a qualifying symptom regardless of whether or not an NP swab was obtained.
Collection of information on SAEs‡‡	At any time during the study period	At any time during the study period	At any time during the study period
Termination record			X

*Each study year, a randomly selected subset of approximately one-third of the subjects provided a blood sample.
†End of each study year was 15 May (+7 days) for each respective season.
‡Information on past influenza and pneumococcal vaccinations.
ℐAfter vaccination, subjects were provided with a memory aid and reminded of the reportable respiratory illness symptoms, which would trigger the need for NP swabbing, as well as the overall active and passive surveillance process.
**Collected from any subject who was identified as having a respiratory illness from Day 14 of vaccination and later. If the respiratory illness started prior to Day 14 from vaccination, a swab did not have to be collected, even in cases where symptoms persisted beyond Day 14.
††Occurrences of any of the following in association with any respiratory illness on or after Day 14 were followed up for 30 days after the illness start date: pneumonia (clinical diagnosis), new onset or exacerbation of pre-existing cardio-respiratory conditions, hospitalizations, ER visits and non-routine medical office visits (including urgent care visits) as well as the diagnoses associated with those instances.
‡‡AESIs were captured as SAEs. These included new onset of GBS, Bell's Palsy, encephalitis, myelitis, optic neuritis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.
Source: CSR FIM 12, Table 3.1, Page 53

A randomly selected subset of approximately one-third of subjects provided a blood sample (10 mL) at Day 28 post-vaccination. Data were used to estimate an HAI correlate of protection against influenza illness caused by each influenza viral type/subtype similar to those contained in the vaccine formulations.

Table 3: FIM12: Study Procedures: Follow Up of Respiratory Illness

Days After Respiratory Illness Onset	Day 0*-Day 4	Day 0-4	Day 30 (+7 days)†
Contact Type	Telephone Call	Visit	Telephone Call
Verify information on respiratory illnesses and schedule appointment for an NP swab within 5 days of illness start date	X		
Remind subject to complete memory aid	X		
Collection of NP swab		X	
Collection of disease burden and health care information	X	X	X
Collection of reportable concomitant medications	X	X	X
Collection of information on respiratory illness symptoms‡	X	X	X

*Day 0 (respiratory illness start date) refers to the first day that the respiratory illness criteria were met (i.e. at least one new or worsening protocol defined respiratory symptom, reported by the subject). For subjects reporting multiple symptoms, if one symptom started before the others, Day 0 was considered the first date of occurrence of the first symptom.
† The 7-day window allowed provision to complete the telephone call. The data collected were inclusive from Day 0 through Day 30 of respiratory illness; information > 30 days from respiratory illness onset did not need to be collected.
‡During collection of information on respiratory illness symptoms, the presence, or not, or concurrent systemic symptoms (i.e. fever, feverishness [feeling of warmth], chill [shivering], tiredness [fatigue], headache, myalgia [muscle aches], nausea, vomiting or diarrhea was also collected.
Source: CSR FIM 12, Table 3-2, Page 54.

The following definitions were used in this study:

Laboratory confirmed influenza was defined as a positive influenza result on either PCR and/or viral culture of a nasopharyngeal (NP) swab sample.

Respiratory illness was defined as the occurrence of a new onset (or exacerbation of a pre-existing condition/symptom) of one or more of the following symptoms (that persisted for or reoccurred after a period of at least 12 hours): sneezing, stuffy or runny nose (nasal congestion), sore throat, cough, sputum production, wheezing or difficulty breathing.

Protocol-defined ILI was determined by the occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: fever (defined as temperature > 99F, chills, tiredness, headache or myalgia.

Modified CDC-defined ILI was defined as the occurrence of fever (defined as temperature > 99ºF with cough or sore throat.

Reviewer Comment: CDC-defined ILI refers to the occurrence of fever (defined as a temperature ≥ 100.0ºF AND cough and/or sore throat (in the absence of a known cause other than influenza). The definition used by Sanofi Pasteur is modified because of the use of a lower cutoff for the definition of fever (temperature > 99ºF).

6.1.7 Endpoints and Criteria for Study Success

The primary efficacy endpoint for the evaluation of efficacy was the occurrence of culture- or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with protocol-defined ILI.

The secondary efficacy endpoints were:

1) Occurrences of culture-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are antigenically similar to those contained in the vaccine formulations, in association with a protocol-defined ILI
2) Occurrences of culture-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a protocol-defined ILI
3) Occurrences of culture-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are antigenically similar to those contained in the vaccine formulations, in association with a modified CDC-defined ILI
4) Occurrences of culture-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a modified CDC-defined IL
5) Occurrences of culture- and/or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are similar to those contained in the vaccine formulations, in association with a protocol-defined ILI
6) Occurrences of culture- and/or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are similar to those contained in the vaccine formulations, in association with a modified CDC-defined ILI
7) Occurrences of culture- and/or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a modified CDC-defined ILI
8) Occurrence of culture and/or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are similar to those contained in the vaccine formulations, in association with respiratory illness
9) Occurrences of culture-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with respiratory illness
10) Occurrences of culture and/or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are similar to those contained in the vaccine formulations, in association with modified CDC-defined ILI

11) Occurrences of culture-and/or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a modified CDC-defined ILI.

6.1.8 Statistical Considerations & Statistical Analysis Plan

Several key elements of the statistical analysis plan are summarized below.

Statistical Method Used to Determine Relative Vaccine Efficacy
The null hypothesis was that relative VE (Fluzone High-Dose compared to Fluzone) was ≤ 9.1%. The null hypothesis was to be rejected and superiority of Fluzone High-Dose demonstrated if the lower bound of the confidence interval for relative VE (Fluzone High-Dose compared to Fluzone) was > 9.1% for the primary objective.

Relative VE was calculated as follows:

Relative VE = 1- $[(C_{HD}/N_{HD)/}C_{FL}/N_{FL})]$

C_{HD} is the number of cases in the Fluzone High-Dose group; N_{HD} is the number of subjects in the Fluzone High-Dose group; C_{FL} is the number of cases in the Fluzone group; N_{FL} is the number of subjects in the Fluzone group.

Missing data were not imputed or replaced and no test for outliers was performed.

An estimated sample size of 30,000 subjects would provide at least 80% power for the primary objective under the following assumptions:

1) The relative VE for Fluzone High-Dose compared to Fluzone was 30% for the primary endpoint.
2) An overall influenza attack rate of 2% for the primary endpoint for the Fluzone Group.
3) A randomization ratio of 1:1
4) Fluzone High- Dose would be considered superior if the lower bound of the CI for the relative VE was > 9.1%
5) 95% of enrolled subjects were evaluable for relative VE

Statistical Method Used to Estimate a Correlate of Protection
The statistical method used to estimate correlates of protection against laboratory-and culture-confirmed influenza for each influenza viral type/subtype in the vaccine was to find a threshold value of HAI that is predictive of the efficacy observed. The protective threshold is such that:

$$\frac{\text{Proportion of Fluzone High-Dose vaccines with HAI titers} < \text{Threshold}}{\text{Proportion of Fluzone vaccinees with HAI titers} < \text{Threshold}} = \frac{\text{Proportion of Fluzone High-Dose vaccines that are cases}}{\text{Proportion of Fluzone vaccinees that are cases}}$$

Interpolation was used to estimate the threshold value of HAI titer precisely solving the estimating equation. For each protective threshold estimate, a 95% two-sided CI was estimated by bootstrapping.

For additional details, please refer to review by Dr. Sang Ahnn, statistical reviewer, OMPT/CBER/OBE/DB/VEB.

6.1.9 Study Population and Disposition

The table below shows the disposition of all subjects enrolled in FIM12 for both years 1 and 2.

Table 4. FIM12: Study Disposition for Years 1 and 2

	Fluzone High-Dose N (%)	Fluzone N (%)	Total
Subjects enrolled and randomized	15991 (100)	15998 (100)	31989 (199)
Subjects vaccinated	15990 (99.99)	15993 (99.97)	31983 (99.98)
Subjects completing the trial	15257 (95.41)	15210 (95.07)	30467 (95.24)
Subjects terminating early	734 (4.93)	788 (4.93)	1522 (4.76)
Reason for early termination			
Lost to follow up	252 (1.58)	280 (1.75)	532 (1.66)
Non-compliance with protocol	167 (1.04)	195 (1.22)	362 (1.13)
Other adverse event	3 (0.02)	1 (0.01)	4 (0.01)
Serious adverse event	102 (0.66)	106 (0.66)	208 (0.65)
Voluntary withdrawal not due to adverse event	210 (1.31)	206 (1.29)	416 (1.30)

Source: Adapted from sBLA 103914/5726; CSR Table 4.1, page 94.

Reviewer Comment: The percentage of subjects who terminated the study early was low (<5%) and equivalent for both study groups. The percentage of subjects terminating due to adverse events (serious and non-serious) was extremely low (< 1%) and consistent between both the Fluzone and Fluzone High-Dose study groups. These data do not raise any concerns pertaining to the study conduct or safety profile of Fluzone High-Dose compared to Fluzone in the population studied.

6.1.9.1 Populations Enrolled/Analyzed

Two analysis sets were used: Full Analysis Set (FAS) and the Per Protocol Analysis Set (PPAS).

The FAS was defined for each study year and comprised those subjects who received study vaccine. The PPAS was a subset of the FAS. Subjects with at least one of the following relevant protocol deviations were to be excluded from the PPAS.

1) Subject did not meet all protocol specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
2) Subject did not receive vaccine
3) Subject received a vaccine that was deemed unacceptable for use
4) Subject received a vaccine other than the one that he/she was randomized to receive

5) Subject's successful surveillance contact was not achieved at least once post Day 28
6) Subject received another seasonal influenza vaccine between study vaccination and end of
7) surveillance the following spring (data collected were taken into account only up to the time the additional seasonal vaccine was received)
8) Subjects with any other protocol deviation identified in the course of study monitoring which, in the opinion of the Sponsor's Responsible Medical Officers based on blinded review, was likely to impact the subject's responses for the primary and secondary endpoints Subject did not receive vaccine
9) Subject received a vaccine that was deemed unacceptable for use
10) Subject received a vaccine other than the one that he/she was randomized to receive
11) Subject's successful surveillance contact was not achieved at least once post Day 28
12) Subject received another seasonal influenza vaccine between study vaccination and end of surveillance the following spring (data collected were taken into account only up to the time the additional seasonal vaccine was received)
13) Subjects with any other protocol deviation identified in the course of study monitoring which, in the opinion of the Sponsor's Responsible Medical Officers based on blinded review, was likely to impact the subject's responses for the primary and secondary endpoints

6.1.9.1.1 Demographics

The demographic information for the treatment groups are summarized in the following table.

Table 5: FIM12: Demographic Characteristics – Full (as treated) Analysis Set

	Fluzone High-Dose N=15992	Fluzone N=15991
Sex n (%)		
Male	6861 (42.9)	7028 (43.9)
Female	9131 (57.1)	8963 (56.1)
Racial Origin n (%)		
White	15106 (94.5)	15164 (94.8)
Asian	118 (0.7)	105 (0.7)
Black or African American	670 (4.2)	612 (3.8)
American Indian or Alaska Native	49 (0.3)	54 (0.3)
Native Hawaiian or Other Pacific Islander	8 (0.1)	10 (0.1)
Mixed Origin	39 (0.2)	43 (0.3)
Ethnicity n (%)		
Hispanic or Latino	957 (5.6)	983 (6.1)
Not Hispanic or Latino	15034 (94)	15007 (93.8)

Source: Adapted from sBLA 103914/5726, CSR FIM12, Table 4.3, page 98.

Reviewer Comment: In both study groups, there was a predominance of females enrolled in the study compared to males. The demographic data do not demonstrate any imbalances in randomization that could affect the safety or efficacy data from this study. The demographic characteristics of subjects in the FAS were similar to those in the PPAS (data not shown).

The majority of subjects in this study were white, non-Hispanic. Although the generalizability of the results of study FIM12 to non-white populations may be considered limited, there are no known differences in the safety or efficacy of inactivated influenza vaccines due to ethnic or racial factors. For subgroup analyses of safety and efficacy by race, age and gender, please see 6.1.11.3.

6.1.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

The majority of subjects had at least one pre-specified chronic comorbidity (67.22% and 67.24% of subjects in the Fluzone High-Dose and Fluzone groups, respectively (FAS as treated cohort). Approximately one-third of subjects had at least 2 pre-specified chronic comorbidities. The most frequently reported pre-specified chronic comorbidities were: diabetes mellitus, hypothyroidism, coronary artery disease, each diagnosis occurring in approximately 18-20% of all subjects. The chronic comorbidities and vaccination history of subjects in the PPAS were similar to those in the FAS (data not shown).

With respect to frailty-associated conditions, hypertension, vision loss and hearing loss were the most frequently reported conditions occurring in approximately 65%, 44% and 27% of subjects respectively, within each study group.

Approximately 40% of the study population reported tobacco use. A small percentage of subjects (<0.7%) were residents of an assisted living facility or nursing home within the last 6 months.

With respect to vaccination history, approximately 93% of subjects in each study group had received a seasonal influenza vaccination in the past.

No imbalances in randomization results that could affect efficacy and/or safety were identified.

Reviewer Comment: The study population represents adults 65 years of age and older, most of whom dwell in the community and have at least one pre-specified comorbidity. The chronic comorbidities and vaccination history of the study population appear to be generally representative of that seen in the general population of adults 65 years of age and older living in the United States, given the prevalence of type 2 diabetes mellitus and coronary artery disease. The study results may have limited generalizability to subjects who reside in nursing homes or assisted living facilities, or subjects who may have low cardiopulmonary reserve or limited muscle mass. The study also may have limited generalizability to vaccine naïve individuals, in whom local reactogenicity may be slightly higher than those with a history of vaccination.

6.1.9.1.3 Subject Disposition

Subject disposition is presented in the following table.

Table 6. FIM12: Disposition of Subjects

	Fluzone High-Dose n (%)	Fluzone n (%)
Subjects enrolled and randomized	15991 (100)	15998 (100)
Subjects vaccinated	15990 (99.99)	15993 (99.97)
Subjects completing trial	15257 (95.41)	15210 (95.07)
Subjects terminating early	734 (4.59)	788 (4.93)
Reasons for early termination		
Lost to follow up	252 (1.58)	280 (1.75)
Non-compliance with protocol	167 (1.04)	195 (1.22)
Other adverse event	3 (0.02)	1 (0.01)
Serious Adverse Events	102 (0.64)	106 (0.66)
Voluntary withdrawal not due to adverse event	210 (1.31)	206 (1.29)

Source: Adapted from sBLA 103914/5726, CSR FIM12, Table 4.1, page 94.

Reviewer Comment: The percentage of subjects who did not complete the trial (< 5%) is within an acceptable range. The percentage of subjects terminated early due to any adverse event is low (<1%). No imbalances between study arms were identified.

6.1.10 Efficacy Analyses

6.1.10.1 Analyses of Primary Endpoint(s)

The results for the efficacy of Fluzone High-Dose relative to Fluzone against laboratory-confirmed influenza caused by any influenza viral types/subtypes, associated with the occurrence of protocol-defined ILI, are shown below.

Table 7. FIM12: Efficacy of Fluzone High-Dose Relative to Fluzone Against Laboratory-Confirmed Influenza Caused by Any Viral Types/Subtypes (Regardless of Similarity to Those Contained in the Vaccine) Combined Years 1 and 2– Per Protocol Analysis Set

	Fluzone High-Dose N=15892 n (%)	Fluzone N=15911 n (%)	Relative Vaccine Efficacy % (95% CI)
Associated with protocol-defined influenza-like illness	227 (1.43)	300 (1.89)	24.24 (9.69; 36.52)
A/H1N1	8 (0.05)	9 (0.06)	11 (-159.9; 70.12)
A/H3N2	171 (1.08)	222 (1.40)	22.88 (5.43; 37.20)
B/Victoria lineage	8 (0.05)	11 (0.07)	27.19 (-98.75; 74.57)
B/Yamagata lineage	24 (0.15)	36 (0.23)	33.25 (-15; 61.91)

Protocol defined influenza-like illness was determined by the occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing or difficulty breathing; concurrently with at least one of the following systemic symptoms: fever (defined as temperature >99.0 F, chills, tiredness, headache or myalgia. Source: Adapted from BLA 103914/5726, CSR Table 5.1, page 102

The pre-specified criterion for demonstration of superiority of Fluzone High-Dose over Fluzone was that the lower bound of the 95% confidence interval (CI) for relative VE > 9.1%. As shown in the preceding table, the primary objective for this study was met (lower bound of 95% CI for relative efficacy was 9.69). The results of this analysis using the Full Analysis Set, were similar. An analysis of the Full Analysis Set showed that the lower bound of the 95% CI for Years 1 and 2 combined also exceeded 9.1% (VE was 24.24%; 95% CI 9.71; 36.50).

An additional analysis, of the same primary endpoint, efficacy of Fluzone High-Dose relative to Fluzone Against laboratory-confirmed influenza caused by any viral types/subtypes using modified CDC-defined ILI as the case-definition, yielded a relative VE of 20.57% (95%CI -4.70; 39.88) (per protocol analysis set).

Reviewer Comment: The estimate of VE for influenza vaccines may vary yearly based on the antigenic similarity between the inactivated influenza viruses contained in the vaccine and the circulating, wild-type influenza virus strains. As shown by the strain-specific analysis of VE, the efficacy of Fluzone High-Dose in this study was driven by efficacy against influenza A/H3N2 strain which appeared to cause the majority of the cases of influenza during the years studied.

FIM12 was conducted over two influenza seasons. In Year 1, the influenza B strain contained in Fluzone High-Dose and Fluzone was of the Victoria lineage. In Year 2, the influenza B strain contained in Fluzone High-Dose and Fluzone was of the Yamagata lineage. The results of the analysis of relative VE by year are shown below.

Table 8. FIM12: Efficacy of Fluzone High-Dose Relative to Fluzone Against Laboratory-Confirmed Influenza Caused by Any Viral Types/Subtypes (Regardless of Similarity to Those Contained in the Vaccine) Year 1–Per Protocol Analysis Set

	Fluzone High-Dose N=7209 n(%)	Fluzone N=7207 N (%)	Relative Vaccine Efficacy % (95% CI)
Associated with protocol-defined influenza-like illness	23 (0.32)	42 (0.58)	45.25 (6.86; 68.57)
A/H1N1	4 (0.06)	6 (0.08)	33.35 (-181.1; 86.17)
A/H3N2	11 (0.15)	25 (0.35)	56.01 (7.32; 80.46)
B/Victoria lineage	2 (0.03)	4 (0.06)	50.01 (-248.8; 95.48)
B/Yamagata lineage	3 (0.04)	2 (0.03)	-49.96 (-1695; 82.82)

Protocol defined influenza-like illness was determined by the occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing or difficulty breathing; concurrently with at least one of the following systemic symptoms: fever (defined as temperature >99.0 F, chills, tiredness, headache or myalgia. Source: Adapted from BLA 103914/5726, CSR Table 5.1, page 102

Reviewer Comment: In study FIM05, the Phase 3 safety and immunogenicity study comparing Fluzone High-Dose to Fluzone (submitted to support licensure of Fluzone High-Dose in 2009 by accelerated approval), superiority criteria were met for both A strains in the analysis of each co-primary endpoint, but not for either B strain comparison. The 95% CI for the HAI GMT ratio of the influenza B strain did, however, meet the non-inferiority criterion (>0.67) (10).The present study, FIM12, was not powered to specifically examine the relative VE of Fluzone High-Dose against influenza B virus contained in the vaccine (B/Victoria). Hence, although the point estimate for relative VE against B/Victoria is 50%, the 95% CI is very wide (95% CI: -248.8; 95.48). Limited cross-protection against B/Yamagata (the strain not contained in the vaccine) appears to be present.

Table 9. FIM12: Efficacy of Fluzone High-Dose Relative to Fluzone Against Laboratory-Confirmed Influenza Caused by Any Viral Types/Subtypes (Regardless of Similarity to Those Contained in the Vaccine) Year 2– Per Protocol Analysis Set

	Fluzone High-Dose N=8683 n (%)	Fluzone N=8704 n (%)	Relative Vaccine Efficacy % (95% CI)
Associated with protocol-defined influenza-like illness	204 (2.35)	258 (2.96)	20.74 (4.39; 34.36)
A/H1N1	4 (0.05)	3 (0.03)	-33.66 (-812.4; 77.39)
A/H3N2	160 (1.84)	197 (2.26)	18.59 (-0.81; 34.33)
B/Victoria lineage	6 (0.07)	7 (0.08)	14.08 (-198.6; 76.14)
B/Yamagata lineage	21 (0.24)	34 (0.39)	38.09 (-9.79; 65.85)

Protocol defined influenza-like illness was determined by the occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing or difficulty breathing; concurrently with at least one of the following systemic symptoms: fever (defined as temperature >99.0 F, chills, tiredness, headache or myalgia. Source: Adapted from BLA 103914/5726, CSR Table 5.1, page 102

The point estimate of calculated relative VE of Fluzone High-Dose compared to Fluzone in the prevention of laboratory-confirmed influenza associated with protocol-defined ILI caused by any viral types/subtypes (per-protocol analysis set) for Year 1 (45.3%) was much higher than the point estimate for Year 2 (20.7%), as shown in Table 8 and 9.

Reviewer Comment: Re-enrollment of Year 1 subjects may have lowered the estimate of relative VE during Year 2.

6.1.10.2 Analyses of Secondary Endpoints

A secondary endpoint of the study was the occurrence of culture-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations in association with a modified CDC-defined ILI, defined as the occurrence of a temperature > 99.0°F (> 37.2°C) with cough or sore throat. The efficacy of Fluzone High-Dose relative to Fluzone for this endpoint was 51.1% (95% CI: 16.8; 72.0).

Table 10. FIM12: Efficacy of Fluzone High-Dose Relative to Fluzone Against Culture-Confirmed Influenza Caused by Viral Types/Subtypes Antigenically Similar to Those Contained in the Vaccine-Combined Years 1 and 2– Per Protocol Analysis Set

	Fluzone High-Dose N=15892 N (%)	Fluzone N=15911 N (%)	Relative Vaccine Efficacy % (95% CI)
Associated with protocol-defined influenza-like illness[1]	63 (0.40)	92 (0.58)	31.44 (4.51; 51.05)
Influenza A	46 (0.29)	63 (0.40)	26.90 (-8.62; 51.13)
A/H1N1	3 (0.02)	3 (0.02)	-0.12 (-647.5; 86.59)
A/H3N2	43 (0.27)	60 (0.38)	28.25 (-7.93; 52.66)
Influenza B	17 (0.11)	29 (0.18)	41.31 (-10.44; 69.74)
B/Victoria lineage	0	0	N/A[3]
B/Yamagata lineage	17 (0.11)	29 (0.18)	41.31 (-10.44; 69.74)
Associated with modified CDC defined influenza-like illness[2]	22 (0.14)	45 (0.28)	51.05 (16.77; 72.01)
Influenza A	17 (0.11)	31 (0.19)	45.10 (-2.32; 71.50)
A/H1N1	0	1 (0.01)	100 (-3805; 100)
A/H3N2	17 (0.11)	30 (0.19)	43.27 (-6.23; 70.65)
Influenza B	5 (0.03)	14 (0.09)	64.24 (-5.06; 89.92)
B/Victoria lineage	0	0	N/A[3]
B/Yamagata lineage	5 (0.03)	14 (0.09)	64.24 (-5.06; 89.92)

[1]Protocol defined influenza-like illness was determined by the occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing or difficulty breathing; concurrently with at least one of the following systemic symptoms: fever (defined as temperature >99.0 F, chills, tiredness, headache or myalgia.
[2]Modified CDC-defined influenza-like illness was defined as the occurrence of fever (defined as temperature > 99.0 F with cough or sore throat.
[3]Relative vaccine efficacy could not be calculated due to lack of influenza cases.
Source: Adapted from BLA 103914/5726, CSR Table 5.2, page 105

When respiratory illness was used as the case definition for ILI, the relative VE was estimated to be 27.88 % (95%CI 3.88; 46.08; data not shown).

Reviewer Comment: The point estimates and lower bounds of the 95% CI for VE were higher when the case definition "modified CDC defined ILI" was used (point estimate 51.05%; 95%CI 16.77; 72.01), rather than "protocol-defined ILI" (point estimate 31.44; 95% CI 4.51; 51.05). The reason for the lower estimate of VE likely reflects differences between the case definitions used for these estimates. In the opinion of this reviewer, the case definition "modified CDC-defined ILI," provides a more specific estimate of influenza cases than the case definition of "protocol defined ILI." Stepwise logistic regression analyses have shown that cough and fever are the clinical factors significantly associated with laboratory-confirmed influenza infection (15, 16). In addition, case definitions of influenza based on the presence of systemic and respiratory symptoms in addition to fever and cough, have been associated with lower positive predictive value in older adults, when compared to the pediatric population and young adults (16). Indeed, the lowest estimate of VE, was obtained when the case definition "respiratory illness" was used. Respiratory illness was the least preferable case definition

because it does not include symptoms (most notably fever and cough) found to be associated with laboratory confirmed influenza infection.

There has been precedent for including data from endpoints pertaining to efficacy against culture-confirmed, vaccine-matched strains in the package insert of other licensed products (17). Although in FIM12, this was a secondary endpoint, this endpoint was pre-specified in the protocol. For this reason, it was considered appropriate to include the results for this endpoint in the package insert for Fluzone High-Dose.

Analyses of additional secondary endpoints listed below (per protocol analysis set) were found to be supportive (Source: STN103914/5276, FIM12 CSR; Table 5.4; page 111).

- relative VE of Fluzone High-Dose compared to Fluzone in the prevention of laboratory-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the vaccine associated with modified CDC-defined ILI (relative VE 48.96% (95%CI: 16.60; 69.45)

- relative VE of Fluzone High-Dose compared to Fluzone in the prevention of laboratory-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the vaccine associated with protocol-defined ILI (relative VE 35.32 (95%CI: 12.42; 52.49).

6.1.10.3 Subpopulation Analyses

Age Subgroups

Post-hoc analyses of relative VE of Fluzone High-Dose compared to Fluzone in the prevention of laboratory-confirmed or culture confirmed influenza associated with protocol-defined ILI, by age subgroups were performed, as shown in the following tables.

Table 11. FIM12: Relative Vaccine Efficacy of Fluzone High-Dose Compared to Fluzone in the Prevention of Laboratory-Confirmed Influenza Associated with Protocol Defined Influenza-Like Illness, By Age Subgroups-Per Protocol Analysis

Efficacy Endpoint	Age (years)	Fluzone High-Dose N=10519 n (%)	Fluzone N=10518 n (%)	Relative Vaccine Efficacy of Fluzone High-Dose % (95% CI)
Laboratory confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	< 75 years	166 (1.47)	193 (1.83)	19.7% (0.3; 35.4)
Laboratory confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	75 to <85	64 (1.36)	96 (2.04)	33.1% (7.3; 52)
Laboratory confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	>85 years	8 (1.19)	11 (1.63)	26.8% (-99.7; 74.5)
Laboratory confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	< 75 years	47 (0.45)	72 (0.68)	34.73 (4.43; 55.79)
Laboratory confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	75 to <85	25 (0.53)	37 (0.78)	32.20 (-15.68; 60.88)
Laboratory confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	>85 years	1 (0.15)	4 (0.59)	74.85 (-154.1; 99.49)

Source: Analysis performed by Dr. Sang Ahnn, Statistical Reviewer, and OBE/Division of Biostatistics/Vaccine Evaluation Branch and by Sanofi Pasteur, adapted from Table 9.130-9.132, Supplemental Tables, and CSR 103914/5726.

Table 12. FIM12: Relative Vaccine Efficacy of Fluzone High-Dose Compared to Fluzone in the Prevention of Culture-Confirmed Influenza Associated with Protocol Defined Influenza-Like Illness, By Age Subgroups-Per Protocol Analysis

Efficacy Endpoint	Age (years)	Fluzone High-Dose N=10519 n (%)	Fluzone N=10518 n (%)	Relative Vaccine Efficacy of Fluzone High-Dose % (95% CI)
Culture-confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	< 75 years	142 (1.35)	173 (1.64)	17.93 (-3.07; 34.73)
Culture-confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	75 to <85	57 (1.21)	84 (1.78)	31.91 (3.55; 52.23)
Culture-confirmed influenza caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) associated with protocol defined ILI	>85 years	6 (0.89)	10 (1.48)	39.64 (-83.29; 81.97)
Culture-confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	< 75 years	40 (0.38)	53 (0.55)	31.04 (-4.95; 55.09)
Culture-confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	75 to <85	22 (0.47)	30 (0.64)	26.42 (-31.90; 59.56)
Culture-confirmed influenza caused by viral types/subtypes similar to those contained in the vaccine associated with protocol defined ILI	>85 years	1 (0.15)	4 (0.59)	74.85 (-154.1; 99.49)

Source: Analysis performed by Dr. Sang Ahnn, Statistical Reviewer, OBE/Division of Biostatistics/Vaccine Evaluation Branch and by Sanofi Pasteur, adapted from Tables 9.138-9.140, Supplemental Tables, CSR 103914/5726.

Reviewer Comment: Due to the small number of subjects in these subgroups, the point estimates shown in the table above are associated with wide 95% CIs. Despite these limitations, these post-hoc analyses demonstrate a trend towards an overall increase rather than a decline in point estimates of VE of Fluzone High-Dose relative to Fluzone associated with increasing age. Some of the analyses also suggest a slight decrease in point estimates of VE of Fluzone High-Dose relative to Fluzone between 74 and 85 years of age, followed by an increase in efficacy in adults > 85 years of age. These trends do not raise a significant concern with respect to the efficacy of Fluzone High-Dose in older adults within each of these subgroups.

Race

A post-hoc analysis of VE of Fluzone High-Dose relative to Fluzone against laboratory confirmed influenza caused by any viral types/subtypes by race (Black/African American, White, and other/unknown racial origin) was limited due to smaller number of subjects in the Black/African-American and other/unknown racial origin subgroups. However, these data did not reveal a trend to suggest lower relative VE in Black/African Americans or subjects of other/unknown racial origin (Source: Tables 9.127-9.129; Per-Protocol Analysis Set; data not shown).

Gender

A post-hoc analysis of relative VE by gender of Fluzone High-Dose relative to Fluzone against laboratory-confirmed influenza associated with protocol-defined ILI caused by any viral type/subtype (primary endpoint) did not demonstrate a difference.

Table 13. FIM12: Efficacy of Fluzone High-Dose Relative to Fluzone against Laboratory-Confirmed Influenza Associated with Protocol Defined Influenza-Like Illness Caused by Any Viral Types/Subtypes by Gender – Per Protocol Analysis Set

Gender	Fluzone High-Dose Males: N=6809 Female: N=9083 n (%)	Fluzone Males: N=6990 Females: N=8921 n (%)	Relative Efficacy % (95% CI)
Male	104 (1.53)	139 (1.99)	23.19 (0.25; 41.01)
Female	123 (1.35)	161 (1.80)	24.97 (4.52; 41.15)

Source: Adapted from Supplemental Tables 9.125-9.126, CSR 103914/5726.

However, a post-hoc analysis of efficacy by gender of Fluzone High-Dose relative to Fluzone against culture-confirmed influenza associated with protocol defined ILI, caused by vaccine matched viral types/subtypes (secondary endpoint), demonstrated higher relative efficacy for females compared to males.

Table 14. FIM12: Efficacy of Fluzone High-Dose Relative to Fluzone against Culture-Confirmed Influenza Associated with Protocol Defined Influenza-Like Illness Caused by Viral Types/Subtypes Antigenically Similar to Those Contained in the Vaccine by Gender– Per Protocol Analysis Set

Gender	Fluzone High-Dose Males: N=6809 Female: N=9083 n (%)	Fluzone Males: N=6990 Females: N=8921 n (%)	Relative Efficacy % (95% CI)
Male	34 (0.50)	33 (0.47)	-5.77 (-76.19; 36.44)
Female	29 (0.32)	59 (0.66)	51.72 (23.48; 70.16)

Source: Adapted from Supplemental Tables 9.149-9.150, CSR 103914/5726.

Reviewer Comment: No significant differences in relative VE by gender were observed in a post-hoc analysis of the results of the primary endpoint were seen (Table 13). However, in a post-hoc analysis of a secondary endpoint, the relative VE of Fluzone High-Dose compared to Fluzone appeared to be higher for females than males. Sex-based differences in humoral immune response and adverse reactions have been observed with other bacterial and viral vaccines, including influenza vaccination (19). For this reason, the significance of the results shown in Table 14 was extensively discussed within CBER. Although the relative VE of Fluzone High Dose compared to Fluzone appears to be higher for females compared to males, study FIM12 was not stratified by gender, and this is a post-hoc analysis of a secondary endpoint. At the same time, the post-hoc analysis of the primary endpoint (shown in Table 13) did not yield similar results, possibly because the case definition for protocol-defined ILI was not as specific. By contrast, the case definition for modified CDC-defined, culture-confirmed, vaccine matched influenza disease is more specific.

No immunogenicity data were submitted with FIM12; HAI titers were obtained in a randomly selected subset subjects 28 days post-vaccination only (no baseline titers obtained).The purpose of obtaining such data was to determine a correlate of protection. However, an analysis of immunogenicity data by gender from the pre-licensure study, study FIM05, a Phase 3, lot consistency, immunogenicity and safety study of Fluzone High-Dose compared to Fluzone in adults ≥ 65 years of age, was performed. The primary objective of the study was to demonstrate lot consistency among 3 lots of Fluzone High-Dose by evaluating immunogenicity. The results of a post-hoc analysis of these immunogenicity data (from FIM05) by gender are shown below.

Table A: FIM05: Immunogenicity of Fluzone High-Dose Compared to Fluzone by Gender (Immunogenicity Analysis Set)

GMT	HAI GMT (95% CI)	HAI GMT (95% CI)	GMT Ratio (95% CI)
	Fluzone High-Dose	Fluzone	
Males	N=1254	N=578	
A/H1N1	103.5 (98; 109.2)	62.5 (57.5; 68.0)	1.65 (1.50; 1.83)
A/H3N2	535.3 (503.2; 569.3)	280.4 (252.8; 311.1)	1.91 (1.70; 2.14)
B	69.6 (66.1; 73.3)	52.1 (47.9; 56.7)	1.34 (1.22; 1.47)
Females	N=1322	N=697	
A/H1N1	129.0 (122.2; 136.1)	71.5 (66.4; 77.0)	1.80- (1.65; 1.98)
A/H3N2	688.6 (650.0; 729.6)	382.8 (349.8; 418.9)	1.80 (1.62; 1.99)
B	68.5 (65.1; 72.1)	52.5 (48.7; 56.6)	1.30 (1.19; 1.43)
Seroconversion	Fluzone High-Dose	Fluzone	Difference
Males			
A/H1N1	43.5 (40.7; 46.3)	17.5 (14.4; 20.9)	25.9 (21.8; 30.1)
A/H3N2	65.4 (62.7; 68.1)	42.8 (38.6; 46.9)	22.6 (17.8; 27.5)
B	37.4 (34.7; 40.2)	25.7 (22.1; 29.5)	11.8 (7.3; 16.3)
Females			
A/H1N1	53.4 (50.7; 56.2)	27.8 (24.5; 31.3)	25.7 (21.3; 30.0)
A/H3N2	72.6 (70.1; 75.1)	57.3 (53.5; 61.1)	15.3 (10.9; 19.7)
B	45.9 (43.2; 48.7)	33.5 (29.9; 37.2)	12.4 (8.0; 16.9)

HAI= hemagglutinin inhibition assay; GMT=geometric mean titer
Seroconversion was defined as pre-vaccination HAI titer < 1:10 and post-vaccination titer of 1:40 OR a pre-vaccination HAI titer of ≥ 1:10 and a minimum four-fold rise post-vaccination.
Source: Adapted from Table 5.10, Appendix 15, Tables 15.2, 15.2, 15.3.

The results demonstrate that, for adults ≥65 years of age, the HAI GMT point estimates are increased in females compared to males, for both Fluzone High-Dose and Fluzone. This effect was observed in immune responses to influenza A strains (A/H1N1 and A/H3N2), but not for the influenza B strain. The 95% CIs associated with these point estimates are not overlapping. The GMT ratio, however, appears to be comparable. The results demonstrate that males mount an increased HAI GMT to Fluzone High-Dose compared to Fluzone, as demonstrated by the fact that the lower bounds of the 95% CIs for the GMT ratios are above 1 for all strains.

Hence, the immunogenicity data from FIM05 support the finding from FIM12 that differences in VE by gender may exist.

6.1.10.4 Dropouts and/or Discontinuations

The Applicant did not replace subjects who were withdrawn. Reasons for withdrawal or dropout had to be clearly documented and the Investigator had to determine whether voluntary withdrawal was due to safety concerns or for another reason. A small percentage (approximately 5%) of subjects terminated the study early. Hence sensitivity analyses were not performed.

6.1.10.5 Exploratory and Post Hoc Analyses

Rates of pneumonia, new onset-or exacerbation of pre-existing cardio-respiratory conditions and health care utilization

Rates of pneumonia, new onset-or exacerbation of pre-existing cardio-respiratory conditions and health care utilization associated with protocol-defined ILI, laboratory-confirmed, caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) for subjects enrolled during both Years 1 and 2 of the study are shown in the following table.

Table 15. FIM12: Rates of pneumonia, new onset-or exacerbation of pre-existing cardio-respiratory conditions and health care utilization associated with protocol-defined ILI, laboratory-confirmed, caused by any viral types/subtypes (regardless of similarity to those contained in the vaccine) Per Protocol Analysis Set

	Fluzone High-Dose N=15892 n (rate)	Fluzone N=15911 n (rate)	Relative Risk (95%CI)
Pneumonia	3 (0.19)	7 (0.44)	0.43 (0.11; 1.55)
New onset or exacerbation of pre-existing cardio-respiratory conditions	46 (2.89)	65 (4.09)	0.71 (0.49; 1.03)
Health Care Visits	147 (9.25)	150 (9.43)	0.98 (0.78; 1.23)
Hospitalizations	6 (0.38)	10 (0.63)	0.60 (0.22; 1.65)
Emergency Room Visits	9 (0.57)	7 (0.44)	1.29 (0.48; 3.46)
Non-routine medical office visits	132 (8.31)	133 (8.36)	0.99 (0.78; 1.26)
Medication Use	233 (14.66)	268 (16.84)	0.87 (0.73; 1.04)
Antipyretics/analgesics/NSAIDS	114 (7.17)	147 (9.24)	0.78 (0.61; 0.99)
Antivirals	22 (1.38)	24 (1.51)	0.92 (0.51; 1.64)
Antibiotics	97 (6.10)	97 (6.10)	1.00 (0.76; 1.33)

Source: Adapted from STN103914/5726, FIM12 CSR, Table 5.5, page 115.

Rates were lower in the Fluzone High-Dose group than in the Fluzone group for pneumonia, new onset or exacerbation of pre-existing cardio-respiratory conditions, hospitalizations, antiviral use and antipyretic/analgesics/NSAID use (point estimates of relative risks < 1). The relative risk was essentially similar for health care visits, emergency room visits, non-routine medical office visits and antibiotics use.

Reviewer Comment: These data do not represent data that could be included in a package insert for Fluzone High-Dose, as these data are limited, post-hoc analyses. Most confidence intervals were wide and crossed 1, indicating lack of statistical significance. Hence these results do not confirm that Fluzone High-Dose improves hospitalization rates, for examples, and are not considered appropriate for labeling.

An analysis of the rates of pneumonia, new onset-or exacerbation of pre-existing cardio-respiratory conditions and health care utilization associated with modified CDC-defined ILI, culture-confirmed, caused by viral types/subtypes similar to those contained in the vaccine (per protocol analysis set) yielded similar results, although the results were limited by insufficient numbers of cases-to calculate relative risk due to more stringent case definition (Source: STN 103914/5726; Table 5.8; Page 121; FIM12 CSR; data not shown).

Correlate of Protection
Definitive conclusions pertaining to an estimated correlate of protection could not be made based on the results from this study due to the wide confidence intervals of the point estimates. The data, however, did suggest that the threshold may vary from year to year and a different threshold for each influenza type/subtype may exist. The number of cases was insufficient to obtain a reliable estimate for the influenza H1N1 subtypes (in both years and overall), the influenza H3N2 subtype in Year 1, and the influenza B type in Year 1. The HAI geometric mean titer estimated to be a threshold for protection by this study for A/Victoria/361/2011 strain (Year 2 H3N2 vaccine component) was 538.58 (95% CI: 139.5; 3550.40); the estimate for the B/Texas/6/2011 strain (Year 2 B vaccine component) was 44.89 (05% CI: 7.47; 287.54). However, for both strains, the 95% CIs were wide. For additional details regarding how the correlate of protection was estimated, please see Section 6.1.8.

Reviewer Comment: These data highlight the limitations in applying HAI titer of 1:40 as a surrogate for protection in older adults for influenza disease, without confirming clinical efficacy. Additional work pertaining to the correlate of protection for influenza in special populations is needed.

6.1.10.6 Conclusions

According to the primary endpoint of FIM12, Fluzone High-Dose was shown to be superior to Fluzone with respect to the prevention of laboratory-confirmed, protocol-defined ILI caused by any viral types/subtypes, regardless of similarity to the vaccine (relative VE 24%; 95%CI:9.69; 36.52). A secondary endpoint of the study also demonstrated superiority of Fluzone High-Dose compared to Fluzone with respect to prevention of culture-confirmed, modified CDC-defined ILI caused by viral types/subtypes similar to those contained in the vaccine (relative VE 31%; 95%CI 4.51; 51.05).

A post-hoc analysis of relative VE by gender demonstrated higher relative VE for females (relative VE 51.72%; 95%CI: 23.48; 70.16) compared to males (relative VE -5.77; 95%CI: -76.19; 36.44). The limitations of this analysis are that it was not pre-specified, and that the study was not stratified by gender.

Post-hoc analyses by age subgroups (<75 years, 75-84 years of age, and < 85 years of age), though limited, did not reveal any trends that would raise concerns regarding the

safety and efficacy of Fluzone High-Dose in these age subgroups. Post-hoc analyses of VE and safety by race did not reveal any significant differences.

6.1.11 Safety Analyses

6.1.11.1 Methods

As the purpose of FIM12 was to provide confirmatory efficacy data to support traditional approval for licensed Fluzone High-Dose, safety was an observational objective of this study. Data on solicited injection site reactions were not collected in this study. Instead, data on SAEs, death, and AESIs were collected.

6.1.11.2 Overview of Adverse Events

Table 16 shows an overview of safety post-vaccination through the end of surveillance.

Table 16. FIM12: Safety Overview Post-Vaccination Through the End of Surveillance – Full (As Treated) Analysis Set

	Fluzone High-Dose N=15992	Fluzone N-15991
Subjects experiencing at least one:	n (%)	n (%)
SAE	1323 (8.27)	1442 (9.02)
Death	83 (0.52)	84 (0.53)

Source: Adapted from Table 6.1, page 151, CSR for STN 103914/5726,

The most frequently reported SAE in both study groups was in the system organ class of cardiac disorders (257 (1.6%) of subjects in the Fluzone High-Dose group; 287 (1.8%) of subjects in the Fluzone group); the most frequently reported event within this system organ class was atrial fibrillation, cardiac failure and myocardial infarction.

Reviewer Comment: Overall no significant imbalances in the number and percentage of SAEs or deaths were seen between the study groups. The types of SAEs observed were consistent with common disorders seen in adults 65 years of age and older. These data do not raise a safety concern associated with Fluzone High-Dose.

Table 17 shows an overview of safety events occurring within 30 days after vaccination.

Table 17. FIM12: Safety Overview Within 30 Days Post-Vaccination– Full (As Treated) Analysis Set

	Fluzone High-Dose N=15992	Fluzone N-15991
Subjects experiencing at least one:	n (%)	n (%)
SAE	204 (1.28)	200 (1.25)
Death	6 (0.04)	0 (0)

Source: Adapted from Table 9.26, page 203, CSR for STN 103914/5726,

Reviewer Comment: Overall no significant imbalances in the number and percentage of SAEs were seen between the study groups. Deaths occurring within 30 days occurred exclusively in the Fluzone High-Dose group, but were determined to be due to chance

as based on a detail review of the narratives for each of these cases (see Section 6.1.11.3).

6.1.11.3 Deaths

Six deaths occurred within 30 days after vaccination. All were in the Fluzone High-Dose group. None of these deaths were considered by the Investigator to be related to vaccination. Each case is described in more detail below:

Subject 011-11147: 73 year old male with a past medical history of congestive heart failure, hypercholesterolemia, atrial fibrillation, hypothyroidism and gout developed an exacerbation of his congestive heart failure b(6) days after vaccination with Fluzone High-Dose. He died the same day, and did not receive therapy for his congestive heart failure.

Subject 064-11057: 74 year old male with a past medical history of hypertension, type 2 diabetes mellitus, hypercholesterolemia, osteoarthritis, slipped and fell while rock climbing in the desert, sustaining blunt force head injury that resulted in his death. The event occurred b(6) days after vaccination with Fluzone High-Dose.

Subject 067-11050: 81 year old male with a past medical history of hypothyroidism, hypertension and type II diabetes mellitus, developed dizziness and confusion on the day of vaccination with Fluzone High-Dose. CT scan of the head showed a large right cerebral hemorrhage with shift and herniation.

Subject 081-12007: 84 year old male with past medical history of chronic obstructive pulmonary disease, type II diabetes mellitus, hypothyroidism, gout and chronic kidney disease, presented to urgent care with cough and vomiting 18 days after vaccination with Fluzone High-Dose. A chest-x-ray showed left lung base opacity indicating pneumonia. The patient was treated empirically with intravenous levofloxacin and methylprednisolone, with improvement in his symptoms and so he was discharged. One week later, the patient fell while at an assisted living facility and did not regain consciousness . He died the same day. An autopsy was not performed.

Subject 204-12135: 78 year old female with a past medical history of pulmonary embolism, right humerus fracture and tonsillectomy sustained flame burns on over 4% of her body and inhaled smoke 12 days after vaccination with Fluzone High-Dose. She was hospitalized and intubated. Her hospital course was complicated by atrial fibrillation, altered mental status and magnetic resonance imaging (MRI) of the brain findings were consistent with hypoxic brain injury and carbon monoxide poisoning. She died while in the hospital.

Subject 226-12093: 72 year old male with a past medical history of myocardial infarction, type II diabetes mellitus, hypercholesterolemia and coronary artery disease status post coronary artery bypass graft, developed a myocardial infarction b(6) days after vaccination with Fluzone High-Dose. The patient died the same day.

Reviewer Comment: The case narratives of each of these deaths were reviewed in detail by this reviewer. Each of these cases was considered unrelated to vaccination by the Investigator. The Investigator's assessment regarding causality of death appears to be reasonable, in the opinion of this reviewer. Four deaths occurred in persons with risk factors for the events leading to death; 2 deaths were accidental. In addition, the causes of death were not the same for these 6 cases. These cases do not represent a safety

concern related to the use of Fluzone High-Dose. The occurrence of 6 deaths within 30 days post-vaccination in the Fluzone High-Dose arm appears to be due to chance.

6.1.11.4 Nonfatal Serious Adverse Events

An analysis of nonfatal SAEs occurring during the entire study period and occurring within 30 days post-vaccination was performed. Nonfatal SAEs attributed to the vaccine by the study vaccine were also evaluated.

Table 18. FIM12: Serious Adverse Events Occurring Within 30 Days of Vaccination with Fluzone High-Dose, by System Organ Class or MEDRA Preferred Term and, Full (As Treated) Analysis Set

System Organ Class	Fluzone High-Dose N=15992	Fluzone N=15991
Infections and infestations	30 (0.19)	37 (0.23)
Cardiac disorders	29 (0.18)	29 (0.18)
Nervous System Disorders	28 (0.18)	23 (0.14)
Musculoskeletal and connective tissue disorders	23 (0.14)	20 (0.13)
Neoplasms	21 (0.13)	18 (0.11)
Gastrointestinal disorders	18 (0.11)	24 (0.15)
General disorders and administration site conditions	14 (0.09)	8 (0.05)
Injury, poisoning and procedural complications	13 (0.08)	12 (0.08)
Respiratory, thoracic and mediastinal disorders	12 (0.08)	14 (0.09)
Vascular disorders	8 (0.05)	6 (0.04)
Renal and Urinary Disorders	7 (0.04)	7 (0.04)
Psychiatric Disorders	2 (0.01)	2 (0.01)
Blood and lymphatic system disorders	2 (0.01)	2 (0.01
Metabolism and nutrition disorders	1 (0.01)	1 (0.01)
Immune System Disorders	1 (0.01)	0 (0)
Surgical and medical procedures	1 (0.01)	1 (0.01)
Reproductive system and breast disorders	0 (0)	2 (0.01)
Total	204 (1.28)	200 (1.25)
Preferred Term		
Drug hypersensitivity	1 (0.01)	0 (0)
Pneumonia	9 (0.06)	11 (0.07)
Nausea	2 (0.01)	0 (0)

Source: Adapted from Table 9.29, page 239, CSR for STN 103914/5726,

Reviewer Comment: No imbalances in the number of unsolicited AEs were seen between Fluzone High-Dose and Fluzone recipients. The most frequently reported unsolicited AEs were: infections and infestations and cardiac disorders, which are medical illness commonly seen in the age group studied. No imbalances in rates of pneumonia were seen between the two groups. In addition, no significant differences in rates of drug hypersensitivity reactions were observed despite the higher antigen content in Fluzone High-Dose.

The results from FIM12 do not indicate an imbalance in the number of gastrointestinal events, including nausea, which was observed in a post-licensure safety surveillance study of Fluzone High-Dose using the VAERS (11). A randomized, double blind,

placebo-controlled study design such as FIM12 constitutes a more powerful study design; the limitations of VAERS analyses include biased reporting, inconsistency in quality and completeness of reports and issues related to over reporting or underreporting. Hence, these data support the safety of Fluzone High-Dose in the population studied.

Three subjects in the Fluzone High-Dose experienced at least 1 non-fatal SAE that was considered possibly related to vaccination by the Investigator. Two of these related SAEs occurred within 30 days after vaccination. None of these related SAEs resulted in discontinuation from the study and all 3 subjects recovered completely. These three cases are described below.

Subject 085-11005: 77 year old female with a past medical history of chronic headaches, stroke, atrial fibrillation, peripheral artery disease, hypercholesterolemia, peripheral neuropathy, hyperthyroidism, thyroid nodule status post left thyroidectomy, breast cancer status post left radical mastectomy, presented to the emergency room with intermittent left sided weakness, left-sided numbness with headache and seizures 117 days after vaccination with Fluzone High-Dose. MRI of the brain showed subarachnoid hemorrhage. EEG showed possible epileptic activity more predominant over the right temporal lobe. The participant was discharged 3 days later. The following day, the participant returned to the emergency room and was readmitted. A MRI of the brain showed minimal signal brightening on diffusion weighted images within both temporal lobes, left temporal parietal region. Right temporal lobe edema was slightly increased. There was also slight increased signal on fluid attenuated inversion recovery images within right rolandic sulcus consistent with subarachnoid blood. Scattered T2 hyperintense signal changes in upper cerebral white matter were also seen, which probably represented chronic microangiopathy. Two days later, the subject was transferred to another hospital where a repeat CT brain showed an asymmetric hypodensity within the right temporal lobe extending to but not involving the grey matter. MRI of the brain was performed, and showed subcortical vasogenic edema in lateral temporal lobes and anterior frontal lobes, and abnormal hypointense T2 signal along right pre and post-central gyrus with adjacent sulcal effacement and hyperemia that might be related to petechial hemorrhage. The radiologist's report suggested the following potential etiologies: possible encephalitis, or unusual demyelinating process, such as acute disseminated encephalomyelitis, progressive multifocal leukoencephalopathy or other viral encephalitis. Lumbar punctures were performed and testing of cerebrospinal fluid was negative for herpes simplex virus infection and by PCR and bacterial meningitis; cryptococcal antigen was negative. Of note, a chest CT performed showed scattered nonspecific nodules measuring less than 5 mm in the left and right upper lobes, bronchiectasis in the right middle lobe with associated lingular and right middle lobe linear scar suspicious for possible atypical mycobacterial infection. The participant was treated with intravenous acyclovir, and oral levetiracetam and fully recovered from her symptoms within the same month.

Reviewer Comment: The sponsor determined that the event was not related to vaccination; the investigator determined that the event was possibly related to vaccination (IND#4518, SN397). In the opinion of this reviewer, it is unlikely that this represents a case of acute disseminated encephalomyelitis related to vaccination for the following reasons: 1) The temporal relationship of the occurrence of this case of possible acute disseminated encephalomyelitis, occurring 117 days post-vaccination, is not consistent with the published literature on this topic. A review of 12 cases of post-

influenza vaccine encephalopathy found that patients typically present within 3 weeks of vaccination (19).
2)The initial symptoms of acute disseminated encephalomyelitis typically include nonspecific symptoms such as headache, fever, lethargy with focal neurologic deficits or cognitive deficits developing gradually (20). This participant's presentation appeared to be acute with focal neurologic deficits (left sided hemiparesis and seizures).which would be consistent with a subarachnoid hemorrhage, which was seen on imaging studies. 3) The participant apparently recovered fully within a month without treatment for acute disseminated encephalomyelitis (intravenous high-dose corticosteroids). Therefore, in the opinion of this reviewer, the clinical data do not provide evidence for a causal relationship between this SAE and vaccination with Fluzone High-Dose.

Subject 213-12026: A 74 year old female, with a past medical history significant for neuralgia of the face and ear, anemia, hypertension, hyperlipidemia, osteoarthritis and gastroesophageal reflux disease, renal insufficiency and lower extremity edema, presented with diplopia and photophobia 1 day post-vaccination with Fluzone High-Dose. An MRI of the brain revealed moderate chronic small vessel ischemic disease and Arnold Chiari Type-1 malformation. Echocardiogram was normal. A neuroophthalmology consultation revealed microvascular left VI cranial nerve palsy and 6 prism-diopter esotropia. The subject completely recovered within 8 weeks.

Reviewer Comment: The Investigator determined that this event was possibly related to vaccination. The most common cause of VI cranial nerve palsy in persons over 50 years of age is microvascular disease (21); this participant clearly had risk factors for microvascular disease (hypertension, hyperlipidemia) and radiographic evidence for microvascular disease on MRI of the brain. Therefore, in the opinion of this reviewer, the clinical data do not provide evidence for a causal relationship between this SAE and vaccination with Fluzone High-Dose.

Subject 223-12080: A 67 year old female with a past medical history of hypertension, osteoporosis, depression, and scleroderma on prednisone, presented with diarrhea, nausea, vomiting associated with hypotension 1 day after vaccination, resulting in hospitalization. The patient was diagnosed with hypovolemic shock in association with a hyponatremia (sodium 130 mEq), hypokalemia (potassium 3.0 mEq), and elevated blood urea nitrogen (20.6 mg/dL). The patient's systolic blood pressure dropped to 60 mm Hg. The patient was treated with norepinephrine, intravenous piperacillin/tazobactam and stress steroids. She fully recovered one week later. The patient then presented to the emergency room again 145 days after vaccination with nausea and vomiting, resulting in hospitalization. She was hydrated and treated with stress steroids with improvement. 203 days post-vaccination, she presented to the emergency room with lightheadedness. Her workup revealed new thrombi in left axillary and subclavian veins. She also had a left upper PICC line which was not infusing total parenteral nutrition. Her blood cultures were positive for coagulase negative Staphylococcus. She was treated with broad-spectrum antibiotics, anticoagulants and intravenous hydration. She fully recovered six days later. The event of hypovolemic shock was reported by the Investigator as related to the investigational vaccine.

Reviewer Comment: The Investigator determined that the event was possibly related to vaccination. Although the Investigator reports the episode of hypovolemic shock occurring one day after vaccination as being related to vaccination, the participant also

had diarrhea, nausea and vomiting significant enough to result in electrolyte abnormalities. In addition, the participant was taking prednisone for scleroderma which could predispose her to adrenal insufficiency, if doses of prednisone were missed.. Therefore, in the opinion of this reviewer, the clinical data do not provide evidence for a causal relationship between this SAE and vaccination with Fluzone High-Dose.

It should be noted, that the SAEs described above are all described in the post-marketing section of the package insert for Fluzone High-Dose.

6.1.11.5 Adverse Events of Special Interest (AESIs)

AESIs (GBS, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, toxic epidermal necrolysis) were captured as SAEs as described in the footnote of Table 2.

The rate of AESIs was 3 (0.02%) in the Fluzone High-Dose group and 6 (0.04%) in the Fluzone group, throughout the study period. The 9 AESIs are described in more detail below.

Reviewer Comment: The rate of AESIs in both study groups appears to be low. No imbalances in the rate of AESIs in both the Fluzone and Fluzone High-Dose group are apparent. These data do not represent a safety concern with respect to AESIs.

Bell's Palsy was reported for 5 subjects in the Fluzone group and 1 subject in the Fluzone High-Dose group. One AESI (a case of Bell's palsy) occurred within 30 days of vaccination; this subject was in the Fluzone group. No AESI led to study termination. All cases were considered not related to the vaccine by the Investigator.

Reviewer Comment: The rate of Bell's Palsy does not appear to be increased in the Fluzone High-Dose group (n=1) compared to the Fluzone group (n=5), despite the higher antigen content contained in Fluzone High-Dose. The rate of Bell's Palsy in this trial overall (6 cases of 30,000) is not higher than the background rate of Bell's Palsy (approximately 30 cases per 100,000 people per year; see reference 22). It should also be noted that the incidence of Bell's Palsy is highest in adults over 70 years of age (22), which consists of the entire study population of FIM12. In addition, most (5 out of 6) cases of Bell's palsy in the trial occurred greater than 30 days post-vaccination.

In the opinion of this reviewer, none of these cases provide substantial evidence regarding the causal relationship between vaccination and the adverse events described. Hence, these data do not represent a safety concern that would require further investigation.

It is important to note, however, that Section 6.2 of the package insert for Fluzone High-Dose and Fluzone currently reports Bell's Palsy as an adverse event spontaneously reported in association with Fluzone. Hence, no further updates to the package insert would be warranted based on the cases of Bell's Palsy observed in this trial.

A case of Stevens-Johnson syndrome occurred in one subject in the Fluzone High-Dose group 167 days after vaccination. This case was considered by the Investigator to be not related to vaccination. This case of Stevens-Johnson syndrome is described below.

Subject 070-11059: A 69 year old male with multiple medical problems including a past medical history of allergy to sulfa drugs, was treated with trimethoprim/sulfamethoxazole for a cellulitis of the left foot, developed a rash that progressed into diffuse blisters covering his body, 166 days after vaccination with Fluzone. A skin biopsy of the lesion indicated bullous pemphigoid. The subject was treated with oral and topical steroids and anti-inflammatory agents which improved the lesions significantly. The subject recovered and discharged 17 days after the first symptom. The Investigator determined that the rash was unrelated to vaccination, and related to the administration of trimethoprim/sulfamethoxazole. 222 days after vaccination, the subject was hospitalized with an episode hypoglycemia associated with an overdose of self-administered insulin, which was determined to be unrelated to vaccination by the Investigator.

Reviewer Comment: In the opinion of this reviewer, this case of Stevens-Johnson syndrome is clearly unrelated to vaccination with Fluzone since the patient was administered an antibiotic from a class of drugs to which he had a known allergy. Of note, Section 6.2 of the package insert for Fluzone High-Dose and Fluzone reports Stevens-Johnson syndrome as an adverse event that has been spontaneously reported in association with these vaccines. The episode of hypoglycemia is also clearly unrelated to vaccination, in the opinion of this reviewer.

One case of acute disseminated encephalomyelitis (Subject 085-11005) is described in further detail in Section 6.1.11.4 under discussion of serious adverse events.

6.1.11.6 Clinical Test Results

No laboratory test results or vital signs were collected during this trial.

6.1.11.7 Dropouts and/or Discontinuations

No imbalances in the percentages of subjects in the Fluzone High-Dose (0.62%) and Fluzone Groups (0.64%) who discontinued the study due to SAEs (most of which were deaths), were observed. Of these SAEs, however, 12 (0.08%) and 2 (0.01%) subjects in the Fluzone High-Dose and Fluzone Groups, respectively, experienced an SAE within 30 days of vaccination. None of these SAEs were considered related to vaccination by the Investigator.

Reviewer Comment: The case narratives for subjects who discontinued the study due to other AEs within 30 days of vaccination were reviewed. In the opinion of this reviewer, these cases were not related to vaccination.

No imbalances in the percentages of subjects in the Fluzone High-Dose (0.02%; n=2) and Fluzone Groups (0.01%; n=1) who discontinued the study due to other AEs were observed.

6.11.11.8 Subpopulation Analyses

Age Subgroups
A post-hoc analysis of safety of Fluzone High-Dose relative to Fluzone by age subgroups (<65 years, 75-84 years and <85 years of age) is shown below.

Table 19. FIM 12: Safety Overview within 30 Days Post-Vaccination by Age – Full (as treated) Analysis Set

<75 Years of Age	**Fluzone High-Dose (N=10580) n (%)**	**Fluzone High-Dose (N=10580) 95%CI**	**Fluzone (N=10564) n (%)**	**Fluzone (N=10564) 95%CI**
SAE[1]	110 (1.04)	0.86; 1.25	111 (1.05)	0.87; 1.26
Death	3 (0.03)	0.01; 0.08	0 (0)	0; 0.03
Adverse Event of Special Interest[2]	0 (0)	0; 0.03	0 (0)	0; 0.03
SAE leading to study discontinuation	7 (0.07)	0.03; 0.14	0 (0)	0; 0.03
Related SAE	2 (0.02)	0; 0.07	0 (0)	0;0.03
Related SAE leading to study discontinuation	0 (0)	0; 0.03	0 (0)	0;0.03
75 to <85 Years of Age	**Fluzone High-Dose (N=4735) n (%)**	**Fluzone High-Dose (N=4735) 95%CI**	**Fluzone (N=4735) n (%)**	**Fluzone (N=4735) 95%CI**
SAE	81 (1.71)	1.36; 2.12	73 (1.54)	1.21; 1.93
Death	3 (0.06)	0.01; 0.19	0 (0)	0; 0.08
Adverse Event of Special Interest	0 (0)	0;0.08	1 (0.02)	0; 0.12
SAE leading to study discontinuation	4 (0.08)	0.02; 0.22	1 (0.02)	0; 0.12
Related SAE	0 (0)	0; 0.08	0 (0)	0; 0.08
Related SAE leading to study discontinuation	0 (0)	0; 0.08	0 (0)	0; 0.08
85 Years of Age and Older	**Fluzone High-Dose (N=677) n (%)**	**Fluzone High-Dose (N=677) 95%CI**	**Fluzone (N=683) n (%)**	**Fluzone (N=683) 95%CI**
SAE	13 (1.92)	1.03; 3.26	16 (2.34)	1.34; 3.78
Death	0 (0)	0; 0.54	0 (0)	0; 0.54
Adverse Event of Special Interest	0 (0)	0; 0.54	0 (0)	0; 0.54
SAE leading to study discontinuation	1 (0.15)	0; 0.82	1 (0.15)	0; 0.81
Related SAE	0 (0)	0; 0.54	0 (0)	0; 0.54
Related SAE leading to study discontinuation	0 (0)	0; 0.54	0 (0)	0; 0.54

[1]SAE = serious adverse event
[2]Adverse Events of Special Interest (AESIs) include Guillain-Barré syndrome, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, toxic epidermal necrolysis
Source: Adapted from Tables 9.114-9.116, Supplemental Tables

Reviewer Comment: As this study is not powered to detect differences on these relatively rare outcomes, slight imbalances in safety are not unanticipated. In the opinion of this reviewer, the post-hoc analysis of safety data 30 days post-vaccination by age subgroup does not raise a significant safety concern related to the use of Fluzone High-Dose as age advances to > 85 years of age.

Additional analyses of safety data 180 days post-vaccination by age subgroup were performed; no significant imbalances in the occurrence of SAEs, AESIs, related SAEs,

or related SAEs leading to study discontinuation were noted (Source: Tables 9.121-9.124, Supplementary Tables, CSR 103914/5726).

Race
A post-hoc analysis of safety within 30 days post-vaccination by race (Black or African American racial origin, White racial origin, and other/unknown racial origin) did not reveal an imbalance between Fluzone High-Dose and Fluzone with respect to SAEs, death, AESIs, SAE leading to discontinuation, or related SAEs (Source: Tables 9.111-9.1113; Full Analysis Set; data not shown).

Gender
A post-hoc analysis of safety within 30 days post-vaccination by gender (male and female) did not reveal an imbalance between Fluzone High-Dose and Fluzone with respect to SAEs, death, AESIs, SAEs leading to discontinuation, or related SAEs (Source: Tables 9.109-9.110; Full analysis set; data not shown).

6.1.12 Study Summary and Conclusions

In summary, no imbalances in the rates of serious adverse events occurring within 30 days or through the end of surveillance were seen when the Fluzone High-Dose group and Fluzone groups were compared. Similarly, no imbalances in the rates of death occurring post-vaccination through the end of surveillance were observed. Although 6 deaths occurred within 30 days of vaccination with Fluzone High-Dose compared to 0 deaths within 30 days of vaccination with Fluzone, this was considered to be due to chance alone, based on a thorough review of the case narratives for each of these deaths. No imbalances in the rates of unsolicited adverse events, in particular, hypersensitivity reactions or gastrointestinal events were seen. The rates of AESIs were low in both the Fluzone and Fluzone High-Dose groups (<0.05%).

In conclusion, the safety data from FIM12 supports the use of Fluzone High-Dose in adults 65 years of age and older.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Fluzone High-Dose is currently labeled Pregnancy Category C because animal reproduction studies have not been conducted with Fluzone High-Dose. This supplement contains no new information pertaining to use of Fluzone High-Dose in pregnancy.

9.1.2 Pediatric Use and PREA Considerations

The present biologics licensing supplement does not trigger the Pediatric Research Equity Act because it does not contain information pertaining to a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration (Section 505B(a) of the Act (21 U.S.C 355)).

9.1.3 Immunocompromised

Post-hoc analyses of safety and efficacy of Fluzone High-Dose compared to Fluzone were performed for immunocompromised subjects—subjects on long-term systemic corticosteroid therapy, subjects with HIV/AIDS, subjects with chronic comorbid immunodeficiency are shown below.

Table 20: FIM 12: Safety Within 30 Days Post-Vaccination for Subjects with Chronic Comorbid Immunodeficiency[1]-Combined Years 1 and 2- Full (as treated) Analysis Set

	Fluzone High-Dose (N=2892) n (%)	Fluzone (N=2835) n (%)
SAE[3]	51 (1.76)	52 (1.83)
Death	1 (0.03)	0 (0)
Adverse Event of Special Interest[2]	0 (0)	0 (0)
SAE leading to study discontinuation	4 (0.14)	0 (0)
Related SAE	1 (0.03)	0 (0)
Related SAE leading to study discontinuation	0 (0)	0 (0)

[1]Chronic Comorbid Immunodeficiency includes subjects with cancer, long-term systemic corticosteroid therapy, HIV/AIDS or potentially immunosuppressive therapy at baseline.
[2]Adverse Events of Special Interest (AESIs) include Guillain-Barré syndrome, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, toxic epidermal necrolysis
[3]SAE = serious adverse event
Source: Adapted from Table 9.161, Supplemental Tables

A subgroup analysis of safety within 30 days of vaccination for subjects within each subgroup listed under "chronic comorbid immunodeficiency (long term systemic corticosteroids therapy, HIV/AIDS, other potentially immunosuppressive therapy, cancer) was consistent with these findings (data not shown).

Reviewer Comment: These post-hoc analyses, though limited, do not raise a significant safety concern associated with the use of Fluzone High-Dose relative to Fluzone in immunocompromised subjects with the conditions listed in the above table. These findings may not apply to subjects with immunocompromising conditions not listed above.

A post-hoc analysis of relative VE in the subgroup of subjects with chronic comorbid immunodeficiency is shown below.

Table 21. FIM12: Efficacy of Fluzone High-Dose Relative to Fluzone against Laboratory-Confirmed Influenza Caused by Any Viral Type/subtypes (regardless of similarity to those contained in the vaccine) for Subjects with any Chronic Comorbid Immunodeficiency[1] – Per Protocol Analysis Set (Years 1 and 2)

	Fluzone High-Dose N=2879 n (%)	Fluzone N=2823 n (%)	Relative Efficacy % (95% CI)
Associated with protocol-defined influenza-like illness[2]	31 (1.08)	51 (1.81)	40.40 (5.05; 63.14)
Associated with modified CDC-defined influenza-like illness[3]	12 (0.42)	21 (0.74)	43.97 (-19.24; 74.87)

[1]Chronic Comorbid Immunodeficiency includes subjects with cancer, long-term systemic corticosteroid therapy, HIV/AIDS or potentially immunosuppressive therapy at baseline.
[2]Protocol-defined influenza-like illness was determined by the occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing or difficulty breathing; concurrently with at least one of the following systemic symptoms: fever (defined as temperature >99.0 F, chills, tiredness, headache or myalgia.
[3]Modified CDC-defined influenza-like illness is defined as the occurrence of fever (defined as temperature > 99.0 F with cough or sore throat.
Source: Adapted from Table 9.164, Supplemental Tables

An analysis of efficacy of Fluzone High-Dose relative to Fluzone against culture-confirmed influenza caused by viral types/subtypes contained in the vaccine for subject with any chronic comorbid immunodeficiency, associated with modified CDC-defined ILI yielded fewer cases of influenza (6 cases in the Fluzone group and 4 cases in the Fluzone High-Dose group), resulting in a calculated VE of 34.63 (-175.7; 86.43).

Reviewer Comment: Although these data do support a trend towards efficacy of Fluzone High-Dose relative to Fluzone in subjects with chronic immunodeficiencies based on point estimates alone, this post-hoc analysis is limited because it is underpowered to evaluate VE, resulting in wide confidence intervals. In addition, 2672 of the subjects included in this analysis in the Fluzone High-Dose group and 2637 subjects in the Fluzone group were subjects with cancer who may or may not have been immunocompromised. Subgroup analyses of other immunocompromised subjects contained in this analysis were limited due to small sample size (data not shown). Therefore, it remains uncertain as to whether the expected immune response and efficacy will be observed if Fluzone High-Dose is administered to immunocompromised persons, including those receiving immunosuppressive therapy, and additional data would be needed to support an indication for use of Fluzone High-Dose in this population.

In conclusion, post-hoc analyses of special populations such as immunocompromised subjects, while limited, support a trend towards efficacy of Fluzone High-Dose in this population, combined with favorable safety profile in terms of SAEs, deaths, AESIs

occurring within 30 days post-vaccination. Limitations of these data include the following: 1) inclusion of subjects with cancer, who may not be truly immunocompromised may overestimate VE and 2) wide confidence intervals for estimates of VE cast doubt on the reliability of these estimates due to small sample size.

10. Conclusions

According to the primary endpoint of FIM12, Fluzone High-Dose was shown to be superior to Fluzone with respect to the prevention of laboratory-confirmed, protocol-defined ILI caused by any viral types/subtypes, regardless of similarity to the vaccine (relative VE 24%; 95%CI:9.69; 36.52). A secondary endpoint of the study also demonstrated superiority of Fluzone High-Dose compared to Fluzone with respect to prevention of culture-confirmed, modified CDC-defined ILI caused by viral types/subtypes similar to those contained in the vaccine (relative VE 31%; 95%CI 4.51; 51.05).

No imbalances in the rates of SAEs, deaths, AESIs occurring within 30 days or through the end of surveillance were seen when the Fluzone High-Dose group and Fluzone groups were compared. No imbalances in the rates of unsolicited adverse events, in particular, hypersensitivity reactions or gastrointestinal events were seen.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 22 summarizes the risk:benefit considerations raised by this supplement.

Table 22: Fluzone High-Dose: Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In the United States (US), an estimated 55,000 to 431,000 hospitalizations and 3,000 to 49,000 deaths are attributed to influenza each year. • During the past 4 influenza seasons in the US, the cumulative hospitalization rate per 100000 adults over 65 years of age was four times higher than that of adults 18-49 years of age. • Adults 65 years of age and older account for the majority (90%) of deaths from seasonal influenza in the US.	• Influenza is a major cause of morbidity and mortality in the US. • A substantial proportion of infections result in serious or life-threatening disease, particularly among high-risk groups such as the elderly.
Unmet Medical Need	• Although 6 licensed, standard dose, inactivated influenza vaccines currently are available to adults 65 years of age and older, immune responses to yearly influenza vaccination is substantially lower in this population, possibly due to decreased T-cell-dependent antibody responses, comorbidities, and functional disabilities observed in this population.	• In adults 65 years of age and older, there is an unmet medical need for effective prevention of influenza infection.
Clinical Benefit	• A double-blind, randomized, clinical endpoint efficacy trial of Fluzone High-Dose compared to Fluzone was submitted to this supplement. • According to the primary endpoint of the study, Fluzone High-Dose was shown to be superior to Fluzone with respect to the prevention of laboratory-confirmed, protocol-defined influenza-like illness caused by any viral types/subtypes, regardless of similarity to the vaccine (relative vaccine efficacy 24%; 95%CI: 9.69; 36.52). • A secondary endpoint of the study also demonstrated superiority of Fluzone High-Dose compared to Fluzone with respect to prevention of culture-confirmed, modified-CDC defined ILI caused by viral types/subtypes similar to those contained in the vaccine (relative vaccine efficacy 31%; 95%CI: 4.51; 51.05).	• The submitted clinical endpoint study verifies clinical benefit of Fluzone High-Dose for the prevention of influenza disease caused by influenza A subtype viruses and type B virus contained in the vaccine in adults 65 years of age and older.
Risk	• Clinical trials pre-licensure did not reveal a significant safety concern associated with the use of Fluzone High-Dose in adults 65 years of age and older. The pivotal study submitted pre-licensure, FIM12, included data from 3837 adults 65 years of age and older, and demonstrated an increase in solicited local and systemic adverse reactions within one week post-vaccination with Fluzone High-Dose compared to the standard formulation (Fluzone). No difference in rates of death and SAEs up to 6 months post-vaccination was observed. • The clinical safety data provided in this supplement, study FIM12, evaluated deaths, SAEs and AESIs of Fluzone High-Dose compared to Fluzone in adults 65 years of age and older. No significant differences in rates of SAEs, deaths and AESIs were observed.	• The evidence indicates that an increase in local and systemic reactogenicity is associated with vaccination with Fluzone High-Dose compared to Fluzone. • The evidence indicates that no increase in risk of SAEs, deaths or AESIs (including anaphylaxis) are associated with vaccination with Fluzone High-Dose compared to Fluzone.
Risk Management	• The most common risks of vaccination (occurring in > 10% of subjects) with Fluzone High-Dose are: injection site pain, injection site erythema, myalgia, malaise and headache. However, the majority of these local and systemic injection site reactions are mild in severity, and resolve within 3 days and without sequelae.	• The package insert and existing pharmacovigilance plan adequately manage these risks.

11.2 Risk-Benefit Summary and Assessment

Data submitted to the BLA supplement establish a substantial likelihood of benefit with respect to two clinically important outcomes in adults 65 years of age and older: 1) prevention of laboratory-confirmed influenza caused by any influenza viral type/subtype in association with ILI and 2) prevention of culture-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the vaccine, associated with modified CDC-defined ILI. As the risks of vaccination with Fluzone High-Dose 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 Recommendations on Regulatory Actions

This reviewer recommends approval of Sanofi Pasteur's supplement to the biologics license application for Fluzone High-Dose, which is indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza subtype A viruses and type B virus contained in the vaccine.

Approval of this supplement fulfills the post-marketing requirement communicated in the December 23, 2009 approval letter to conduct an active-controlled clinical endpoint efficacy study that verifies the superior clinical benefit of Fluzone High-Dose compared to Fluzone in adults 65 years of age and older.

11.4 Labeling Review and Recommendations

Revisions to the package insert discussed with the Applicant are described below.

In Section 6 of the package insert for Fluzone High-Dose, the Applicant had included a description of 3 SAEs which the Investigator, but not the Sponsor had determined to be related to vaccination with Fluzone High-Dose. The case narratives for each of these serious adverse events were reviewed in detail (as described in Section 6.1.11.4 of this review). In the opinion of this reviewer, the level of evidence for causality did not appear sufficient to include these cases in the package insert. This was discussed with the Applicant who removed these cases from the package insert, with concurrence from the review committee.

In Section 14 of the package insert for Fluzone High-Dose, the Applicant had only included the results for the primary endpoint of the study, occurrence of laboratory-confirmed influenza (as determined by culture or polymerase chain reaction) caused by any influenza viral type/subtype in association with a protocol-defined influenza-like illness. In the opinion of this reviewer and the review committee, the results of the secondary pre-specified efficacy objective, efficacy of Fluzone-High-Dose relative to Fluzone against culture-confirmed influenza caused by influenza viral types/subtypes antigenically similar to those contained in the vaccine, associated with the occurrence of a modified CDC-defined ILI), was an endpoint appropriate for labeling. The preference for this endpoint was communicated to the Applicant on August 25, 2011, prior to submission of this BLA supplement.

11.5 Recommendations on Postmarketing Actions

No changes to the existing pharmacovigilance plan for Fluzone High-Dose are recommended based on the information contained in this supplement.