Summary Basis of Regulatory Action

Date: April 30, 2015

To: Wellington Sun, MD, DVRPA Director

Through: Rakesh Pandey, Ph.D., DVRPA Branch Chief
Tim Nelle, Ph.D., DVRPA Team Lead

From: Goutam Sen, Ph.D., DVRPA, Committee Chair

BLA/ STN: 103914/5752

Applicant Name: Sanofi Pasteur Inc. Swiftwater, PA 18370

Date of Submission: June 30, 2014

PDUFA Goal Date: April 30, 2015

Proprietary Name: Fluzone®

Established Name: Influenza Virus Vaccine

Indication: Fluzone is a vaccine for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B virus contained in the vaccine for use in persons 6 month of age and older.

Dosage Forms: Suspension for injection supplied in 2 presentations; prefilled syringe (clear plunger rod), 0.5 mL; multi-dose vials, 5 mL.

Recommended Action: Approval

Signatory Authorities Action: Approval

Division Signatory Authority: Wellington Sun, M.D., Director, Division of Vaccines and Related Product Applications

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

The documentation used as the basis for the content of the various disciplines covered in this SBRA is listed in the table below.

Specific documentation used as basis for the SBRA	**Reviewer – Date of Review**
Clinical Review	Melissa Del Castillo, M.D. – 04/30/15
CMC/Product Review	Vladimir Lugovtsev, Ph.D. – 03/27/15
Statistical Review, Clinical	Sang Ahnn, Ph.D. – 03/30/15
Biomedical Monitoring	Dennis Cato – 03/24/15
Labeling	Sonny Saini, Pharm.D. – 11/18/14
Communication and Documentation	Haiyan (Rebekah) Qin Ph.D. - 04/30/15

Cross-referenced Applications:

- IND 4518 -Influenza Virus Vaccine, Trivalent, Types A & B, (split virus components), Licensed (Connaught, Inc.) sponsored by Sanofi Pasteur Inc.
- IND 8578 - Influenza Virus Trivalent Types A and B, Purified Subvirion Vaccine (chicken embryo; Fluzone) sponsored by Sanofi Pasteur Inc.
- IND 11775 - Influenza Virus Vaccines, Inactivated (Fluvirin; Evans; Fluzone; Aventis; chick embryo) and Influenza Virus Vaccine, Live (FluMist; MedImmune; chick embryo) sponsored by NIAID/NIH.
- IND- 14078- Influenza Virus Quadrivalent (A(H1N1)/A(H3N2)/B(Yamagata)/B(Victoria); split virus; chicken eggs) Vaccine, Inactivated, sponsored by Sanofi Pasteur Inc.

1. Introduction

Fluzone, a split virion, trivalent seasonal influenza vaccine (TIV), contains the purified outer membrane protein hemagglutinin (HA), from each of the 3 influenza virus strains recommended annually by the World Health Organization (WHO) and the Vaccines and Related Biological Products Advisory Committee (VRBPAC). The Fluzone HA antigens are derived from viruses propagated in embryonated chicken eggs. Fluzone is approved for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B virus contained in the vaccine for use in persons 6 month of age and older.

This prior approval supplement was submitted to add clinical efficacy data to the Fluzone Prescribing Information (PI) for children 6 through 24 months of age and adults 18 through 49 years of age.

2. Background

Since early 2010, CBER and Sanofi Pasteur have been discussing various proposals to update the Fluzone Trivalent (TIV) label with clinical efficacy data. Agreement was reached that the

efficacy data to be provided would be derived mainly from external clinical studies. This submission is the culmination of the negotiations and agreements between Sanofi Pasteur and CBER and is a presentation of efficacy data from two clinical studies for inclusion in the existing Fluzone TIV label. The first, designated as Study 593-04, was a randomized, double-blind, placebo-controlled study that was conducted at a single US center during the 1999-2000 and 2000-2001 influenza seasons under IND 8578. The primary endpoint of this study was evaluation of rates of acute otitis media (AOM) among children vaccinated with Fluzone as compared to placebo, and one of the secondary endpoints was to evaluate the vaccine efficacy of Fluzone compared to placebo over two influenza seasons. The second, designated as Study GRC70, was a randomized, multi-center, double-blind, placebo-controlled trial conducted throughout the 2007–2008 influenza season (November to April) under IND 11775. The study was sponsored by the Applicant and conducted by investigators at the University of Michigan. The results presented by the Applicant in the clinical study report was published by the University of Michigan investigators who conducted the study (Monto AS, Ohmit SE, Petrie JG, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. N Engl J Med. 2009; 361: 1260-7). Neither study was originally conducted to support labeling changes. The data were re-analyzed by Sanofi Pasteur biostatisticians using company-written standard operating procedures (including primary analysis using the per-protocol population as opposed to the intent-to-treat population that was reported in the publication). The Per protocol population included all enrolled participants who were randomized, vaccinated and who provided all three planned blood specimens within the study year. In contrast, the Intent-to-Treat Analysis Set consisted of all enrolled participants who were randomized and vaccinated. Because the data did not differ significantly between the PP and ITT, the ITT analysis was used in the Fluzone label.

3 Chemistry Manufacturing and Controls (CMC)

No CMC information was provided in this supplement.

4. Nonclinical Pharmacology/Toxicology

No toxicology studies were performed in support of the current supplement.

5. Clinical Pharmacology

No clinical pharmacology or pharmacokinetic studies were performed in the development program for FluLaval.

6. Clinical Effectiveness and Safety

6.1.1 Efficacy of Fluzone in Children 6 through 24 Months of Age

Study 593-04 was a randomized, double-blind, placebo-controlled study conducted at a single US center (Children's Hospital of Pittsburg, CHP) during the 1999-2000 (Year 1) and 2000-2001 (Year 2) influenza seasons. Participants received two doses of either Fluzone (N = 525) or a placebo (N = 261). The Per protocol (PP) population included any child who received

two doses of study vaccine, and was evaluated at least once every 30 days during the "respiratory season", and once every 60 days during the non-respiratory season. The Intent-to-Treat Analysis (ITT) Set consisted of all enrolled participants who were randomized and received at least one vaccination. The intent-to-treat analysis set included a total of 786 children 6 through 24 months of age. Among all randomized participants in both years, the mean age was 13.8 months; 52.5% were male, 50.8% were Caucasian, 42.0% were Black, and 7.2% were of other racial groups. Cases of influenza were identified through active and passive surveillance for influenza-like illness or acute otitis media and confirmed by culture. Influenza-like illness was defined as fever (tempretaure of at least 38^{o}C) with signs or symptoms of an upper respiratory infection. The definition of ILI differs slightly from the Centers for Disease Control definition of ILI (fever and a cough and/or sore throat). However, the definition used in the study was fever and any symptom of upper respiratory tract infection (URTI), which was broader, and use of this definition should have had greater sensitivity in detecting cases of influenza. Vaccine efficacy against all influenza viral types and subtypes was a secondary endpoint and is presented in Table-1. However, no information is provided in the present submission regarding the antigenic similarity between viruses cultured from study participants, viruses circulating in the community, and the strains contained in the vaccine.

Table 1: Study 593-04 -Estimated Efficacy of Fluzone Against Culture-Confirmed Influenza in Children Aged 6 through 24 Months during the 1999-2000 and 2000-2001 Influenza Seasons – Intent-to-Treat Analysis Set

	Fluzone				Placebo				Fluzone vs. Placebo	
Year	n	N	Rate (n/N)	(95% CI)	n	N	Rate (n/N)	(95% CI)	Relative Risk (95% CI)	% Vaccine efficacy (95% CI)
Year 1 (1999-2000)	15	273	5.5	(3.1; 8.9)	22	138	15.9	(10.3; 23.1)	0.34 (0.18; 0.64)	66 (36; 82)
Year 2 (2000-2001)	9	252	3.6	(1.6; 6.7)	4	123	3.3	(0.9; 8.1)	1.10 (0.34; 3.50)	-10 (-250; 66)

As shown in Table-1, the efficacy of Fluzone in preventing culture-confirmed influenza (all subtypes) was demonstrated during Year 1 with an attack rate of 15.9% in the placebo group and 5.5% in the Fluzone group for vaccine efficacy of 66%. However, efficacy was not demonstrated in Year 2; this was most likely related to the low attack rates in both arms when only four subjects in the placebo group were diagnosed with influenza disease. During the 1999-2000 season, the CDC reported that influenza type A (H3N2) was the predominant strain circulating in the United States. The predominant strain nationwide in 2000-2001 was influenza A (H1N1). The circulating influenza strains during the 1999-2000 and 2000-2001 seasons were well matched to the strains included in the vaccines for their respective years.

6.1.2 Safety outcomes:

The only safety data collected were serious adverse events (SAEs). SAEs were collected from the day of vaccination to the end of follow up. One SAE in the Fluzone group was considered by the investigator to be related to vaccination. Subject No. 346, a 13-month-old female, developed a staring episode. This staring episode was only described as "brief" and occurred on the day of vaccination with no other explanation and therefore was considered related. It resolved, with no diagnosis of seizure. There were no deaths during the study.

6.2.1 Efficacy of Fluzone in Adults

GRC-70 was a randomized, double-blind, placebo-controlled study conducted at a single US center (University of Michigan) during the 2007-2008 influenza season. The study is available at ClinicalTrials.gov under NCT 00538512. Healthy adult volunteers from 18 through 49 years of age received one dose of either Fluzone vaccine (N = 813), an active comparator (N = 814), or placebo (N = 325). Cases of influenza were identified through active and passive surveillance and confirmed by cell culture and/or RT-PCR. Influenza-like illness was defined as an illness with at least 1 respiratory symptom (cough or nasal congestion) and at least 1 constitutional symptom (fever or feverishness, chills, or body aches). The primary endpoint of the study was to evaluate the efficacy of Fluzone against culture confirmed influenza disease influenza season.

The intent-to-treat analysis set included 1138 healthy adults who received Fluzone or placebo. Among all participants mean age was 23.3 years; 63.3% were female, 83.1% were Caucasian, and 16.9% were of other racial/ethnic groups.

Vaccine efficacy of Fluzone against any influenza viral types and subtypes is presented in Table 2. Data provided in the current submission did not include efficacy or attack rate by influenza strain or by matched and mismatched strains. Information was provided for all cases due to any influenza A and all cases due to influenza B. Influenza A subtype and B type were identified by sequencing and not by serologic testing.

Table 2: Study GRC70 Estimated Efficacy of Fluzone Vaccine Against Influenza in Adults Aged 18 through 49 Years during the 2007-2008 Influenza Season – Intent-to-Treat Analysis Set

Laboratory-Confirmed Symptomatic Influenza	Fluzone (N=813)			Placebo (N=325)			Fluzone vs. Placebo	
	n	Rate (%)	(95% CI)	n	Rate (%)[f]	(95% CI)	Relative Risk (95% CI)	% Vaccine efficacy (95% CI)
Positive culture	21	2.6	(1.6; 3.9)	31	9.5	(6.6; 13.3)	0.27 (0.16; 0.46)	73 (54; 84)

Laboratory-Confirmed Symptomatic Influenza	Fluzone (N=813)			Placebo (N=325)			Fluzone vs. Placebo	
	n	Rate (%)	(95% CI)	n	Rate (%)[f]	(95% CI)	Relative Risk (95% CI)	% Vaccine efficacy (95% CI)
Positive PCR	28	3.4	(2.3; 4.9)	35	10.8	(7.6; 14.7)	0.32 (0.20; 0.52)	68 (48; 80)
Positive culture, positive PCR, or both	28	3.4	(2.3; 4.9)	35	10.8	(7.6; 14.7)	0.32 (0.20; 0.52)	68 (48; 80)

In Study GRC70, vaccine efficacy was demonstrated for Fluzone compared to placebo for any influenza strain, matched or mismatched to the vaccine strains. The attack rate was 3.4% in the Fluzone arm and 10.8% in the placebo arm; absolute vaccine efficacy for Fluzone was 68% (lower bound confidence interval of 48%), as assessed via either culture or RT-PCR.

6.2.2 Safety Outcomes

The only safety data collected were serious adverse events (SAEs). A total of 11 subjects reported SAEs during the study: 8 subjects in the Fluzone group and 3 subjects in the placebo group. Incidence rates were similar in the two groups. None of the SAEs were considered related to vaccination. There were no deaths during the study.

6.3 Statistical Review - Summary of Results

Since the purpose of this submission is to update the Fluzone PI, the absolute efficacy of the comparator vaccine, or the relative efficacy comparing two vaccines (Fluzone vs. the comparator vaccine) was not included in the Clinical Study Report for GRC70. Although the PP population is typically used for the primary analysis of vaccine efficacy, but since the data did not differ dramatically between PP and ITT in both studies, the ITT analysis was used in the Fluzone label. Based on the agreement between the applicant and CBER, the applicant proposed to include in the package insert information on the, absolute efficacy of Fluzone in adults 18-49 years of age (Table-2 in this review) and in children 6-24 months of age (Table-1 in this review).

The absolute efficacy of Fluzone was estimated as one minus the relative risk of culture-confirmed influenza in the Fluzone vaccination group compared to the placebo group. The relative risk (RR) was calculated by comparing the cumulative incidence (incidence proportion) of cases in the Fluzone group to the cumulative incidence of cases in the placebo group: $RR = P_v/P_p$ where P_v and P_p are the risk estimates (or observed proportion of cases) in Fluzone and placebo groups, respectively. Exact 2-sided 95% CI for the absolute efficacy was constructed using Clopper-Pearson's method. There was no success criterion for the study. No formal statistical hypothesis was tested.

6.4 Clinical Assays

The description of the laboratory techniques used in both clinical trials (provided as SOPs for specimen processing, virus detection, identification, and human serology studies) were reviewed. Since the clinical studies were not originally intended to be included in the Fluzone package insert, the laboratory techniques were not thoroughly validated. Nonetheless, the laboratory procedures were well-defined and performed under standardized and controlled conditions by qualified experts in the field. Therefore, the laboratory procedures were deemed adequate and valid for measuring the efficacy of the vaccine.

6.5 Pediatric Research Equity Act (PREA)

This supplement did not trigger a PREA assessment because it does not involve a new indication, new active ingredient, new dose form, new dosing regimen or new route of administration.

6.6 Biomonitoring Review

One clinical site associated with Study Protocol 593-04 and two clinical sites for Study Protocol GRC70 were inspected. The bioresearch monitoring inspections did not reveal problems that impact the data submitted in this supplement.

6.7 Advisory Committee Meeting

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting because review of this submission did not identify concerns which would have benefitted from an advisory committee discussion.

7. Labeling

The prescribing information (PI) was reviewed by the clinical reviewer and reviewers from the Advertising and Promotional Labeling Branch. The major changes to the PI were as follows:

- Package Insert:
  - *Clinical Studies* (section 14): A brief description of the 593-04 and GRC-70 clinical efficacy studies with results in tabular form (Table 3 and 4) has been included.

After negotiations with the sponsor, the committee concurred that version 0.3 of the package insert submitted March 20, 2015 is acceptable.

8. Recommendations and Risk/Benefit Assessment

8.1 Recommended Regulatory Action

Following the review of all supportive product and clinical data, the review committee recommends approval of this BLA supplement to include efficacy data in the prescribing information.

8.2 Risk/ Benefit Assessment

The clinical efficacy information submitted in this supplement supports the safety and effectiveness of Fluzone when administered to persons 6 months of age and older. The clinical review of the submission did not find any new safety signals or an unexpected increase in SAEs in the two clinical studies (GRC70 and 593-04). The risk-benefit profile of Fluzone remains favorable for use in the prevention of influenza.

8.3 Summary of Recommendations

The data in this supplement supports the effectiveness of Fluzone in adults 18 – 49 years of age and in children 6 – 24 months of age based on the two efficacy clinical studies (GRC70: in adults 18 – 49 years of age and 593-04: in children 6 – 24 months of age) and the results should be included in the Fluzone prescribing information, section 14.1 and 14.2.