

Summary Basis for Regulatory Action

Date: October 30, 2014

From: CDR Edward W. Wolfgang, MSA, Chair of the Review Committee

BLA/ STN: 103914/5726

Applicant Name: Sanofi Pasteur Inc.

Date of Submission: December 30, 2013

Proprietary Name/ Established Name: Fluzone[®] High-Dose (Influenza Vaccine)

Indication: Fluzone[®] High-Dose is an inactivated influenza vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus A subtype viruses and type B virus contained in the vaccine. Fluzone High-Dose is approved for use in persons 65 years of age and older.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, DVRPA

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

Specific documentation used in developing the SBRA	Reviewer Name – Document Date
Clinical Review	Roshan Ramanathan, M.D., M.P.H 10/29/14
Statistical Review	Sang Ahnn, Ph.D. 08/25/14
CMC Review	Vladimir Lugovtsev, Ph.D. 05/28/14
Labeling Reviews	CDR Sonny Saini, Pharm.D., MBA 08/25/14, Roshan Ramanathan, M.D., M.P.H. 10/29/14
Regulatory Communication, Coordination, and Documentation	Haiyan Qin, Ph.D., M.P.H., Regulatory Project Manager Goutam Sen, Ph.D., Regulatory Project Manager

1. INTRODUCTION

On March 2, 2009, Sanofi Pasteur Inc. (U.S. License 1725) submitted a supplement to their Biologics License Application (sBLA) for Influenza Vaccine for a high dose formulation under the Accelerated Approval regulations (21 CFR 601.41). The submission was approved on December 23, 2009, and included a postmarketing requirement for Sanofi to conduct a required clinical study, to verify and describe clinical benefit. In response to that study requirement, Sanofi Pasteur Inc. submitted on December 30, 2013, a prior approval supplement (BL 103914/5726) containing a Clinical Study Report for a post-marketing randomized clinical study, FIM12, “Efficacy Study of Fluzone High-Dose Vaccine Compared with Fluzone Vaccine in Adults \geq 65 Years of Age” along with the virological and serology methods used in the study to update the Fluzone High-Dose prescribing information. With this supplement approval Sanofi Pasteur Inc. has fulfilled the post-marketing requirement to verify clinical benefit, allowing the conversion of Fluzone High-Dose vaccine from accelerated approval status to traditional approval.

2. BACKGROUND

The original confirmatory trial agreed upon between CBER and Sanofi Pasteur, Study FIM07, was a clinical endpoint efficacy and safety study of Fluzone High-Dose compared to Fluzone. Study FIM07, initiated in 2009, and was intended to be conducted over a three-year period in approximately 30,000 adults 65 years of age and older. During the first year of the trial, the 2009-2010 influenza season, approximately 9,000 subjects were enrolled. Among study subjects, 22 laboratory confirmed (20 positive by culture and 22 positive by polymerase chain reaction) cases of influenza were identified, of 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. CBER agreed to postponing continuation of the trial during the 2010-2011 influenza seasons because of the atypical epidemiology of influenza.

In a May 31, 2011, in discussions with Sanofi, CBER agreed that the first year of the FIM07 trial could be un-blinded and the analysis of the trial could be performed. CBER also agreed that the FIM07 trial could be terminated and that Sanofi Pasteur could conduct the required confirmatory efficacy trial under a different trial protocol (FIM12). It was agreed that the new study, FIM12 would replace the study FIM07 that was to be conducted under the original postmarketing requirement. FIM12 was completed after being conducted over 2 influenza seasons with nearly 32,000 subjects enrolled in the United States and Canada. On December 30, 2014, Sanofi submitted a prior approval supplement (PAS) containing a final study report with clinical data to the Biologics License for “Influenza Vaccine Fluzone®” to update the prescribing information with clinical endpoint efficacy data and to close out the postmarketing requirement.

3. CHEMISTRY, MANUFACTURING, AND CONTROL INFORMATION

With the clinical data submitted, Sanofi Pasteur Inc. included virological and serology methods used in the clinical study. Summary information that described the main characteristics and performance of assays utilized to test samples from subjects enrolled in clinical study FIM12. For each assay, a description of the principle, justification and procedure for each serological assay was provided.

Included in the description of the assay procedure is a description of critical materials, references (reference standard for determining concentration or reference serum for ensuring assay validity), quality controls, calculation methods, and assay validity criteria.

A review of the qualification/validation or suitability information for the serological assays demonstrates that the assays were appropriate and suitable for the intended use in the evaluation of clinical samples. Diagnostic testing was performed for virus identification and serological testing was performed to measure antibody responses. All testing was performed at various external testing laboratories under the direction of Sanofi Pasteur's Global Clinical Immunology (GCI) Department, Swiftwater, Pennsylvania. The information provided for virological and serological methods and assays was determined to be acceptable.

4. CLINICAL PHARMACOLOGY

No clinical pharmacology data were provided in the supplement.

5. CLINICAL/ STATISTICAL

Sanofi Pasteur Inc. addressed the requirement to conduct a post-approval study to verify and describe the anticipated clinical benefit of a product licensed under the accelerated approval regulations by conducting FIM12, a postmarketing, randomized, modified double-blind, active-controlled, multi-center trial in adults \geq 65 years of age. The trial was conducted at 126 sites in the United States and Canada. The primary efficacy objective was to compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in adults \geq 65 years of age, with respect to laboratory-confirmed influenza (as determined by culture or polymerase chain reaction), caused by any influenza viral types/subtypes, associated with the occurrence of influenza-like illness (ILI). ILI was determined by 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 $>99.0^{\circ}\text{F}$, chills, tiredness, headaches or myalgia.

The study met the pre-specified criterion for demonstration of superiority of Fluzone High-Dose over Fluzone (lower bound of the 95% CI was $>9.1\%$). The efficacy of Fluzone High-Dose relative to Fluzone for the primary endpoint was 24.2% (95% CI: 9.7; 36.5).

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 $> 99.0^{\circ}\text{F}$ ($> 37.2^{\circ}\text{C}$) 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).

A CBER analysis by gender showed that the relative efficacy of Fluzone High-Dose to Fluzone against culture-confirmed influenza associated with protocol defined influenza-like illness caused by virus antigenically similar to those contained in the

vaccine was higher in females than in males. However this difference was not seen with analysis using the primary endpoint.

6. SAFETY

A review of the safety results from study report FIM12 indicated no increase in the serious adverse events, adverse events of special interest, or rates of deaths associated with the Fluzone High Dose vaccination compared to Fluzone.

7. ADVISORY COMMITTEE MEETING

It was determined that the discussion of the review of the sBLA for Fluzone High-Dose by the Vaccines and Related Biological Products Advisory Committee was not required because of CBER's experience with the currently licensed Fluzone and Fluzone High-Dose products. Furthermore, our review of information submitted in the supplement, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

8. LABELING

Review of the prescribing information identified deficiencies, most of which required only minor modifications to the text. After negotiations with the sponsor, it was determined by the committee that the revised prescribing information for Fluzone[®] High-Dose submitted under this supplement was acceptable.

9. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

The review team made a determination that no postmarketing commitments or postmarketing requirements were needed.

The committee recommends approval of the sBLA.