Summary Basis for Regulatory Action

Date: December 23, 2009

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

LCDR Jeremy L. Wally, Ph.D., Regulatory Project Manager

BLA/ STN: 103914/5240

Applicant Name: Sanofi Pasteur Inc.

Date of Submission: March 2, 2009

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

Indication: Fluzone® High-Dose is an inactivated influenza virus vaccine indicated for 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.

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	Therese Cvetkovich, M.D. 12-07-09
Pharmacovigilance Review	Trish Rohan, M.D. 12-11-09
Statistical Review	Sang Ahnn, Ph.D. 11-16-09
CMC Review	Zhiping Ye, M.D., Ph.D. 12-17-09
CMC/Facility/ Establishment Inspection Report Reviews	Chiang Syin, Ph.D. 11-04-09, 11-18-09
Lot Release	Joe Quander III 12-17-09 Rajesh Gupta, Ph.D. 12-23-09
Biomonitoring Review	Bhanumahti Kannan 11-24-09
Labeling Reviews	Maryann Gallagher 08-03-09, 11-05-09 LCDR Jeremy L. Wally, Ph.D. and CDR Edward W. Wolfgang 12-17-09, 12-23-09

1. INTRODUCTION

On March 2, 2009, Sanofi Pasteur Inc. (US License 1725) submitted a supplement to their Biologics License Application (sBLA) for Influenza Virus Vaccine for a high dose formulation under the Accelerated Approval regulations. The proprietary name Fluzone® High-Dose was proposed. Fluzone® High-Dose contains 60 mcg HA antigen per virus strain (A/H1N1, A/H3N2, and B) for a total of 180 mcg hemagglutinin (HA) per dose. Fluzone® High-Dose is provided as an unpreserved sterile solution in single-dose (0.5 mL) syringes and is to be administered intramuscularly. Fluzone® High-Dose is intended for the immunization of the elderly (65 years of age and older) to elicit enhanced immune responses against influenza through higher antigen content.

2. BACKGROUND

Fluzone® High-Dose is a high dose formulation of an inactivated influenza virus vaccine, for intramuscular use, prepared from influenza viruses propagated in embryonated chicken eggs. The Fluzone® High-Dose manufacturing process closely follows the procedures used for the applicant's currently licensed product Fluzone®, but it is modified in that gelatin is eliminated as a stabilizer and a different concentration factor is used to concentrate ----b(4)---------- after the ultrafiltration step in order to obtain a higher HA antigen concentration.

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 hemagglutination inhibition (HI) antibody titers after administration of Fluzone High-Dose or standard dose Fluzone to individuals 65 years of age and older. This 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 approval under the accelerated approval regulations (21 CFR 601 Subpart E). According to these regulations, the applicant must confirm the clinical benefit of the product with due diligence.

Chemistry, Manufacturing, and Control Information

Fluzone® High-Dose influenza virus vaccine is a sterile suspension prepared from influenza viruses propagated in embryonated chicken eggs. Fluzone® High-Dose vaccine is formulated to contain 180 mcg hemagglutinin (HA) per dose, in the ratio of 60 mcg HA antigen of each of the three prototype H1N1, H3N2 and B strains. The Fluzone® High-Dose manufacturing process closely follows the procedures used for the applicant's currently licensed product Fluzone® with the exception that gelatin is not used in the manufacturing process for Fluzone® High-Dose. No thimerosal is used in the manufacturing process for Fluzone® High-Dose.

Description and Characterization

Prior to formulation of the trivalent bulk Drug Product, -----b(4)----------
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Nomenclature for Drug Substance

Full Name	Alternative Names
Influenza Virus (H1N1), *strain specified*, HD Split Virion Zonal Concentrate, No Preservative	-----b(4)---------- -----b(4)---------- -----b(4)---------- -----b(4)----------
Influenza Virus (H3N2), *strain specified*, HD Split Virion Zonal Concentrate, No Preservative	-----b(4)---------- -----b(4)---------- -----b(4)---------- -----b(4)----------
Influenza Virus B/ *strain specified*, HD Split Virion Zonal Concentrate, No Preservative	-----b(4)---------- -b(4)---------- -----b(4)---------- -b(4)----------

The manufacturing process for the HD Influenza Drug Substance utilizes similar process steps and controls as the current Fluzone® manufacturing process. The process parameters are defined during process validation and controlled through the Batch Production Record. These process parameters are listed in the following table.

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[b(4)]

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[b(4)]

b) CBER Lot Release

A Testing Plan for Fluzone® High-Dose was developed by the Division of Product Quality in OVRR with concurrence from the review committee. Product testing was performed on final bulk and all specifications were met. The product cannot be distributed without written approval from CBER.

Completed lot release protocols were reviewed and approved by CBER. For routine lot release, the firm will submit to CBER samples from final bulk and a Lot Release Protocol for each lot. Fluzone® High-Dose will be released by CBER on final bulk test results.

c) Facilities review/inspection

A decision was made to waive the pre-approval inspection because of CBER's manufacturing and safety experience with the currently licensed product Fluzone®, the fact that Fluzone® High-Dose manufacturing process closely follows the procedures used for Fluzone®, and no issues arose that necessitated such an inspection based on the criteria outlined in CBER SOPP 8410 "Determining When Pre-Licensing/Pre-Approval Inspections (PLI/PAI) are necessary."

e) Environmental Assessment

Sanofi submitted a request for categorical exclusion from an environmental assessment under 21 CFR 25.31(c). CBER reviewed this information and determined the product falls into the category of substances that occur naturally in the environment and the action (approval of the sBLA) would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. The categorical exclusion from an environmental assessment was accepted.

3. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Given the extent of human experience with Fluzone® nonclinical data were not required to support this sBLA.

4. CLINICAL PHARMACOLOGY

No clinical pharmacology data were provided in the supplement.

5. CLINICAL/ STATISTICAL

A phase 3 clinical study, FIM05, constitutes the principal clinical database supporting the sBLA for use of Fluzone® High-Dose in the elderly population aged 65 years and older. FIM05 was a multicenter, prospective, randomized comparison of immune responses after vaccination with Fluzone® High-Dose or standard dose Fluzone conducted in 3,837 subjects 65 years of age and older. FIM05 was conducted in the target population, adults 65 years of age and older, at the proposed marketed dose, 180 µg HA total/0.5 mL administered IM. The study was designed to demonstrate an effect on a surrogate endpoint likely to predict clinical benefit. The results of Study FIM 05 also provided substantial evidence to support the safety of Fluzone® High-Dose in an elderly population.

The demonstration of equivalent hemagglutination inhibition (HI) assay Geometric Mean Titers (GMTs) among recipients of each of the three lots of high dose formulation in study FIM05 provided evidence supporting consistency of manufacturing of Fluzone® High-Dose and justified combining the results from the three lot groups in order to conduct subsequent pre-specified evaluations of HI titers and safety data in the Fluzone® High-Dose groups compared to the standard Fluzone group. The co-primary endpoints for the comparative immunogenicity

evaluation were seroconversion rates (SCR) and GMTs. The pre-specified superiority criteria were met for both A strains in the analysis of each co-primary endpoint, but not for either B strain comparison. For each A strain, the lower limit of the 95% CI for the GMT ratio [Fluzone HD/ Fluzone] met the prespecified limits of > 1.5. Likewise, for SCR, the lower limit of the 95% CI for the difference between Fluzone HD and Fluzone met the prespecified margin of > 10% for each A strain. The B strain, while not meeting superiority criteria, met non-inferiority criteria, for GMT ratio (> 0.67), and for SCR difference (> -10%). These results support the superiority of HI antibody responses to Fluzone® High-Dose in people 65 years of age and older compared to standard Fluzone®, as predefined in the study protocol.

The safety evaluation in Study FIM05 included data from the 3,837 elderly adult subjects who received either Fluzone High Dose (2,575) or standard dose Fluzone (1,288); these data did not reveal any unexpected Serious Adverse Events (SAEs) or other adverse events. Rates of death and SAEs documented during the six months duration of the study were comparable between the two groups. Solicited local and systemic adverse events documented during the week after vaccination supported phase 2 data in which increased local and systemic reactogenicity was increased after vaccination with the high dose formulation compared to the standard formulation. These events occurred more frequently and tended to be of greater severity in those randomized to the Fluzone® High-Dose group. The duration of these events were similar between the two groups.

Prior to submitting this sBLA, the sponsor agreed to conduct a large, randomized, multicenter, multiyear clinical endpoint efficacy and safety study (FIM07) in which rates of culture confirmed influenza after vaccination with Fluzone® High-Dose or standard dose Fluzone® in 27,000 – 30,000 elderly adults will be evaluated. This study has been initiated and the first 9,000 subjects have been enrolled and vaccinated. Based upon review of the clinical data submitted in this sBLA, approval under accelerated approval regulations (21 CFR 601 Subpart E), outlining the use of a surrogate endpoint that is reasonably likely to predict the clinical benefit of the biologic product, is recommended.

Under FDA's Compliance Program Guidance Manual 7348.811, Inspection Program for Clinical Investigators, three clinical investigators in Study FIM05 were inspected. The inspections focused on specific questions concerning clinical protocols submitted. Some exceptions were noted and Voluntary Action Indicated letters were issued, but no significant problems were found to impact the data submitted in the sBLA.

6. SAFETY

Adverse events graded as moderate to severe occurred more often in the Fluzone High-Dose group compared to standard dose Fluzone. The rates of reported solicited reactions (fever, headache, malaise, myalgia) and injection sites reactions (swelling, erythma and pain) in the Fluzone High-Dose group tended to be higher as compared to the control group but were generally mild in nature.

7. ADVISORY COMMITTEE MEETING

It was determined that review of the sBLA for Fluzone® High-Dose by the Vaccines and Related Biological Products Advisory Committee was not required because of CBER's manufacturing and safety experience with the currently licensed Fluzone® product and because Fluzone® High-Dose manufacturing closely follows the procedures used for the current licensed Fluzone® product.

8. OTHER RELEVANT REGULATORY ISSUES

CBER found out-of-specification (OOS) -b(4)- batch results at the 2-month time point and OOS results for -b(4)- potency for two batches of B/Malaysia strains at the 9 and --b(4)--- time points. Because of the OOS results, CBER did not agree with Sanofi's request for a --b(4)----- expiry for final container and requested additional stability information. Based on this submitted information and negotiations with Sanofi, CBER agreed instead to a 9-month expiry for final container. To address the -b(4)- profile in stability, Sanofi has implemented an evaluation of a ---b(4)---------- for Fluzone® High-Dose.

9. LABELING

The proprietary name Fluzone® High-Dose was approved by the Advertising and Promotional Labeling Branch. The carton and syringe labels were reviewed and found to be acceptable. Review of the prescribing information (PI) identified numerous deficiencies, most of which required only minor modifications to the text. After negotiations with the sponsor, it was determined by the committee that the prescribing information for Fluzone® High-Dose is acceptable.

10. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

Sanofi committed to two post marketing commitments.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

1. ----b(4)----------

Accelerated Approval Required Study

2. Sanofi Pasteur Inc. agrees to submit the results of the ongoing Study No. 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. If the attack rate of influenza in a season is lower than expected, participant enrollment will be extended to an additional season. The final study report for three seasons will be submitted by February 2013.

The committee recommends approval of the sBLA.