Summary Basis for Regulatory Action

Date: May 9, 2011

From: LCDR Jeremy L. Wally, Ph.D., Chair of the Review Committee
CDR Edward W. Wolfgang, Regulatory Project Manager

BLA/ STN: 103914/5369

Applicant Name: Sanofi Pasteur Inc.

Date of Submission: July 9, 2010

Proprietary Name/Established Name: Influenza Virus Vaccine/Fluzone® Intradermal

Indication: Fluzone Intradermal is an inactivated influenza virus vaccine administered intradermally and indicated for active immunization of persons 18 through 64 years of age 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	Karen Farizo, M.D.
Pharmacovigilance Review	David Menschik, M.D., M.P.H.
Statistical Review	Sang Ahnn, Ph.D.
CMC Review	Zhiping Ye, M.D., Ph.D.
CMC/Facility/Establishment Inspection Report Reviews	Donald Ertel Nicole Trudel
Toxicology Review	Claudia Wrzesinski, D.V.M.
Lot Release	Joe Quander III
Biomonitoring Review	Dennis Cato
Device Consultant Review	Sajjad H. Syed, Ph.D.
Labeling Reviews	Maryann Gallagher Karen Farizo, M.D.

1. INTRODUCTION

On April 15, 2010, Sanofi Pasteur Inc. (US License 1725) submitted a supplement to their Biologics License Application (sBLA) for Influenza Virus Vaccine to be administered intradermally as a combination product under the traditional approval process. The proprietary name Fluzone Intradermal was proposed. Fluzone Intradermal contains 9 mcg hemagglutinin (HA) antigen per virus strain (A/H1N1, A/H3N2, and B), for a total of 27 mcg HA per dose, in a 0.l mL Becton Dickinson (BD) ---(b)(4)---- MicroInjection System single-use syringe for intradermal administration and is intended for the immunization of adults (18 to 64 years of age).

2. BACKGROUND

Fluzone Intradermal is a sterile suspension prepared from influenza viruses propagated in embryonated chicken eggs. The virus is harvested from the allantoic fluid, inactivated with formaldehyde, concentrated, purified in a linear sucrose density gradient solution using a continuous flow centrifuge, and finally chemically disrupted using a non-ionic surfactant, Octylphenol Ethoxylate (Triton® X-100) to produce a "split virus". This split virus is then further purified and suspended in sodium phosphate-buffered isotonic sodium chloride solution. The upstream manufacturing processing of Fluzone Intradermal is identical to that for Fluzone High-Dose, and differ only in the formulation of the final bulk to a lower concentration per mL in order to achieve a 9 mcg HA per strain dose at a volume of 0.1 mL and a change in the container closure system to the BD --(b)(4)--- MicroInjection System single-use syringe.

Clinical evaluation of Fluzone Intradermal included two pivotal studies conducted in adults 18 through 64 years of age: Study FID02, a Phase 2, dose-ranging safety and immunogenicity study of Fluzone Intradermal; and Study FID31, a Phase 3, lot-consistency, immunogenicity, and safety study in which Fluzone Intradermal was compared to Fluzone. Additional safety and immunogenicity data from Study FID33, a revaccination study of a subset of participants from Study FID31, was also included, as well as supportive safety data from US Studies FID04, FID29, and FID21 in elderly subjects (using a higher dose) and in European Studies GID02 and GID15 of Intanza in adults. Data from Study FID30 in which adults completed a self-administered questionnaire to indicate their preference for intradermal or intramuscular vaccination was also included, as well as safety and immunogenicity data on Fluzone Intradermal and Fluzone from a Phase 2 pediatric study (Study FID07) to support the sponsor's request for a waiver of pediatric studies under the Pediatric Research Equity Act (PREA).

3. CHEMISTRY, MANUFACTURING, AND CONTROL INFORMATION

Fluzone Intradermal influenza virus vaccine is a sterile suspension prepared from influenza viruses propagated in embryonated chicken eggs and formulated to contain 27 mcg HA per dose, in the ratio of 9 mcg HA antigen of each of the three H1N1, H3N2 and B viruses. The Fluzone Intradermal manufacturing process is identical to that of Fluzone High-Dose, and differ only in the formulation of the final bulk to a lower concentration per mL in order

to achieve a 9 mcg HA per strain dose at a volume of 0.1 mL and a change in the container closure system to the BD --(b)(4)-- MicroInjection System single-use syringe. Antibiotics are not used during the manufacture of Fluzone Intradermal, and neither the preservative thimerosal nor gelatin is added to the vaccine.

Drug Substance

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Drug Product
The Fluzone Intradermal Drug Product is formulated by ----------(b)(4)---------- vaccine strength of 9 mcg of HA per strain/0.1 mL dose for a total of 27 mcg HA/0.1 mL dose with ----------(b)(4)---------- bulk Fluzone Intradermal Drug Product formulation is performed in Building (b)(4) the sponsor's Swiftwater, Pennsylvania site, the same facility used to produce Fluzone final formulated trivalent bulk. There were no facility or utility changes (WFI, Clean Steam, Compressed Air or HVAC) due to the introduction of the Fluzone Intradermal process.

Filling, inspection, assembly, labeling, and packaging of Fluzone Intradermal are performed in Building (b)(4) at the sponsor's ----(b)(4)---- site. This site is registered and was inspected by the FDA in May 2007. However, as information pertaining to the ---------

(b)(4) site is new to the Fluzone license, facility, utility and equipment information as well as process flow diagrams were provided in the submission. Changes to the flow of product, personnel, equipment and waste were not necessary for the implementation of Fluzone Intradermal filling.

Container Closure
The Drug Product is filled into BD --(b)(4)-- MicroInjection System syringes, which are --(b)(4)-- BD (b)(4) glass syringes configured with 30-gauge affixed stainless steel 1.5 mm intradermal needles, and external non-fluid path needle shielding systems that incorporate needle guards to shield the needles after completion of the injection.

Description of Manufacturing Process
The final bulk formulation manufacturing process consists of combination of the three monovalent concentrates, ----------(b)(4)---------- of 9 mcg of HA per strain/0.1 mL dose for a total of 27 mcg HA/0.1 mL dose, mixing and filtration. Each formulation of the bulk of Fluzone Intradermal is based on the required HA concentration. The final drug product is then filled into BD -(b)(4)- MicroInjection System syringes. The final containers are inspected and released according to site procedures and master specifications, and then authorized by Sanofi Pasteur Quality Assurance Unit for shipment. Finished Fluzone Intradermal is shipped and stored at 2-8ºC.

Process Validation
The Fluzone Intradermal Drug Product manufacturing process, including formulation, shipping, filling, and aseptic processing, has been validated to produce the vaccine to predetermined specifications. The manufacturing process is consistently capable of producing a product that meets the safety, purity, potency and quality requirements.

Control of Excipients
The excipients used in the manufacture of drug product, Fluzone ID Subunit Vaccine are: Sodium Chloride, Sodium Phosphate –(b)(4)- and Sodium Phosphate ---(b)(4)---- As all of the analytical procedures are identical to those used for Fluzone and comply with the (b)(4), validation was not performed.

Specifications
The batch release acceptance criteria for the Drug Product are given in the following tables:

Acceptance Criteria for the Fluzone Intradermal Drug Product Bulk

Test	Acceptance Criteria
Sterility	No Growth
----(b)(4)------	----------(b)(4)----------
----------(b)(4)----------	----------(b)(4)----------
-------(b)(4)----------	----------(b)(4)----------
---(b)(4)----	------(b)(4)----------
(b)(4)	---(b)(4)----
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Acceptance Criteria for the Fluzone Intradermal Final Container (Unlabeled)

Test	Acceptance Criteria
Sterility	No Growth
Major A Defects	--------(b)(4)--------- ---------(b)(4)---------- ---------(b)(4)--------

Acceptance Criteria for the Fluzone Intradermal Final Container (Labeled)

Test	Acceptance Criteria
Volume Check	------(b)(4)------
Major B Defects	------------(b)(4)----------- -------(b)(4)---------
Final Identity --------(b)(4)--------	Identifies with influenza strains

Stability

----------(b)(4)----------

Two studies were conducted to test the stability of the Fluzone Intradermal Drug Product final container. In the first study, acceptance criteria for pH, physical exam, (b)(4) potency, sterility, and general safety testing were met through (b)(4) months at 2-8°C. In the final study, acceptance criteria for pH, physical exam, sterility, general safety testing, volume, ----------(b)(4)------- testing were met through (b)(4) months, but (b)(4) potency was observed to -----(b)(4)-------- resulting in out of specification results for two out of three batches at the 9, --(b)(4)--- month time points and all three batches at the ---(b)(4)--- month time points for the B/Florida strain. Based upon these studies, the proposed expiry for the Fluzone Intradermal Drug Product final container is 9 months. Annual stability studies of Fluzone Intradermal will take place post licensure.

CBER Lot Release

A testing plan for Fluzone Intradermal was developed by the Division of Product Quality with concurrence from the review committee, and product testing was performed on final bulk with all specifications being met. Completed lot release protocols were reviewed and approved by CBER. For routine lot release, the sponsor will submit samples from final bulk along with a Lot Release Protocol, and Fluzone Intradermal will be released by CBER based upon final bulk testing results.

Facilities Review/Inspection

A pre-approval inspection of the sponsor's -----(b)(4)------ site was conducted as part of review of this supplement because filling, inspection, assembly, labeling, and packaging of Fluzone Intradermal are performed in Building (b)(4) at this site. The main focus of the

inspection was the validation of the aseptic filling process and qualification of the associated equipment and facilities. The scope also included, but was not limited to, the auditing of quality systems, support systems, and materials management. CBER issued an 11 item Form FDA 483 on 15 Feb 2011. The firm did not contest any of the observations and has since provided an adequate response. All inspectional issues have been resolved.

Environmental Assessment
The sponsor 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.

Device Review
The BD -(b)(4)- MicroInjection System syringe was reviewed via a CDRH consult under the Fluzone Intradermal supplement to the Fluzone license, since Fluzone Intradermal is a combination product. The testing performed by the sponsor showed that the syringe filled with Fluzone Intradermal is compatible and stable through study of leachables and extractables. Testing performed by the device manufacturer includes clinical trials to support that their syringe performs according to its specifications, biocompatibility and sterility testing to support that they conform to the Agency's recognized ISO standards, and a Human Factors User Evaluation study to the prove safe and effective usability of the syringe.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The sponsor submitted one reproductive-developmental toxicity study and two local toxicity studies in ----------(b)(4)-------- rabbits. All studies were conducted under Good Laboratory Practice (GLP) regulations. In the reproductive and developmental toxicity study, rabbits received either saline or one human dose of Fluzone Intradermal twice before mating and on gestation day 6 and 27, or Fluzone Intradermal twice before mating and on gestation day 12 and 27. Rabbits then either underwent Caesarean section on day 29 post-coitum and were submitted for embryotoxicity evaluations, or were allowed to litter. There were no treatment-related effects on the reproductive performance, no test-article-related-effects in terms of the pre- and post-implantation data, fetal weight or sex (no association was found between vaccine treatment and incidences of soft tissue and skeletal anomalies and their variations), and no test article-effects were reported on pup survival (from birth to weaning), pup weight, pup sex or physical development. Based on these data, intradermal administration of Fluzone Intradermal containing 27 μg HA per dose did not produce any maternal or developmental toxicity in ---------(b)(4)-------- rabbits. Hence, pregnancy category B has been recommended.

In one local toxicity study, female ---------(b)(4)-------- rabbits received one human dose of Fluzone Intradermal on study day 0, 14 and 28 intradermally or of Fluzone intramuscularly on day 0 followed by an intradermal injection of one human dose of Fluzone Intradermal

on study day 14 and 28, with each injection administered at a unique site. On study days 31 and 42, a necropsy was performed and the histopathology of the injection site was evaluated. Injection-site reaction in vaccinated animals consisted of mild to moderate dermal inflammation with mixed cell infiltration which was of reduced severity and frequency after the recovery phase. Animals receiving Fluzone Intradermal showed mild erythema and edema, and minimal induration. In the second local toxicity study, female ----------(b)(4)-------- rabbits received Fluzone Intradermal at a dose of either 21 or 15 µg HA/strain on study days 0, 14 and 27 or 15µg HA/strain of Fluzone on study day 0 intramuscularly followed by 21µg HA/strain Fluzone Intradermal on study days 14 and 27, with each injection administered at a unique site. On study days 30 and 41, a necropsy was performed and the histopathology of the injection site was evaluated. Injection-site reaction consisted of moderate to marked dermal inflammation with mixed cell infiltration which was of reduced severity and frequency after the recovery phase. Animals showed a moderate to marked edema, mild erythema and minimal induration; all Draize scores returned to baseline before the end of the recovery phase.

5. CLINICAL PHARMACOLOGY

No clinical pharmacology data were provided in the supplement.

6. CLINICAL/ STATISTICAL

Two pivotal studies were conducted in adults 18 through 64 years of age: Study FID02, a Phase 2, dose-ranging safety and immunogenicity study of Fluzone Intradermal; and Study FID31, a Phase 3, lot-consistency, immunogenicity, and safety study in which Fluzone Intradermal was compared to Fluzone. Safety and immunogenicity data from Study FID33, a revaccination study in which a subset of participants from Study FID31 received Fluzone Intradermal or Fluzone in the subsequent year, was also included. Supportive safety data was also provided from US Studies FID04, FID29, and FID21 in which elderly persons received Fluzone Intradermal formulated with a different antigen content than that intended for licensure, as well as European Studies GID02 and GID15 of Intanza in adults. The safety data from these studies are considered supportive in the evaluation of the safety of Fluzone Intradermal for use in adults 18 through 64 years of age. Additional clinical data submitted includes data from Study FID30 in which adults 18 through 49 years of age completed a self-administered questionnaire to indicate their preference for intradermal or intramuscular vaccination prior to and after vaccination with Fluzone Intradermal and Fluzone on the same day, and safety and immunogenicity data on Fluzone Intradermal and Fluzone from a Phase 2 pediatric study (Study FID07) in US infants and children 6 months through 8 years of age. The sponsor submitted results of the Study FID07 to support their request for a waiver of pediatric studies under the Pediatric Research Equity Act (PREA). In all of the Fluzone Intradermal clinical studies submitted, Fluzone Intradermal was administered using the BD -(b)(4)- MicroInjection System syringe.

Lot Consistency

In Study FID31, based on pre-specified criteria, lot consistency across three lots of Fluzone Intradermal was demonstrated in terms of post-vaccination hemagglutination inhibition (HI) antibody GMTs for influenza strains A/H1N1, A/H3N2, and B.

Immunogenicity

Based on pre-specified criteria, in Study FID31, non-inferiority of Fluzone Intradermal relative to Fluzone was demonstrated in terms of HI antibody GMTs for influenza virus strains A/H1N1, A/H3N2, and B, and in terms of seroconversion for strains A/H1N1 and A/H3N2. Non-inferiority was not demonstrated for seroconversion to influenza B (UL of 95% CI for difference Fluzone minus Fluzone Intradermal, 11.3, was above the pre-specified margin of 10). In secondary analyses, the proportions of subjects with HI antibody titers $\geq$1:40 for each strain post-vaccination were similar in the Fluzone Intradermal and Fluzone groups. In descriptive immunogenicity analyses in Study FID31, females who received Fluzone Intradermal had somewhat lower post-vaccination HI antibody GMTs for each of the three strains than males; seroconversion rates were generally similar in females and males. Immune responses (GMTs and seroconversion rates) following Fluzone were generally similar in females and males. Leakage at the injection site of Fluzone Intradermal was observed relatively infrequently (4.6% of subjects in Study FID31). In Study FID31, immune responses (HI antibody GMTs, seroconversion rates, and proportion of subjects with titers $\geq$1:40) to Fluzone Intradermal did not appear to be diminished in subjects who had injection site leakage, with the possible exception of GMTs and seroconversion rates for strain A/H3N2, although the analyses were limited by the small number of subjects with injection site leakage.

In Study FID02, Fluzone Intradermal was shown to be non-inferior to Fluzone in terms of GMTs for all three strains. In secondary analyses from this study, seroconversion rates for each of the strains were similar following Fluzone Intradermal and Fluzone. The proportion of subjects with an HI antibody titer $\geq$1:40 post-vaccination was similar between groups for influenza strains A/H3N2 and A/H1N1, but marginally lower in the Fluzone Intradermal group for influenza strain B (76.2% vs. 81.4%; UL of 95% CI for difference Fluzone minus Fluzone Intradermal, 11).

In Study FID33, previous vaccination with Fluzone Intradermal did not appear to adversely affect immune responses to a dose of either Fluzone or Fluzone Intradermal in the subsequent year.

Preference for Fluzone Intradermal or Fluzone

In Study FID30, prior to vaccination, but after viewing the Fluzone Intradermal delivery system and the Fluzone syringe and needle, approximately two-thirds of subjects ages 18 through 49 years of age indicated a preference for the intradermal device. During the period 0 through 7 days following vaccination with both Fluzone Intradermal and Fluzone in opposite arms on the same day, approximately one-third of subjects indicated a preference for intradermal vaccination.

PREA
The Supplement included the report of a Phase 2 clinical trial (FID07) in which the safety and immunogenicity of Fluzone Intradermal was compared to that of Fluzone in children ages 6 months through 8 years. In the trial, the safety of Fluzone Intradermal was evaluated in 97 children 6 months through 35 months of age, and in 160 children 3 years through 8 years of age. Consistent with studies of Fluzone Intradermal in adults, in Study FID07, Fluzone Intradermal was associated with increased local reactogenicity relative to Fluzone. The study was of insufficient size to reliably evaluate the occurrence of serious adverse events following Fluzone Intradermal in children 6 months through 8 years of age. The study was underpowered for the primary immunogenicity analyses, and it is difficult to draw conclusions about the immune response to Fluzone Intradermal in children from this study. The review Division does not consider Study FID07 as fulfilling the requirement, under PREA, for a pediatric assessment.

The applicant requested a full waiver of pediatric studies of Fluzone Intradermal, based in part, on the failure to meet some of the non-inferiority criteria for the primary immunogenicity analyses of Fluzone Intradermal relative to Fluzone in Study FID07. While the review Division does not consider Study FID07 as adequate to draw conclusions about the immune response to Fluzone Intradermal in children, a full waiver of pediatric studies of Fluzone Intradermal is recommended based on the following rationale: For infants <6 months of age, Fluzone Intradermal provides no meaningful therapeutic benefit over vaccination beginning at 6 months of age and is not likely to be used by a substantial number of infants in this age group. Available data indicate that the immune response to inactivated influenza vaccines in infants <6 months of age is not as robust as in older children due to immaturity of the immune response and interference from maternal antibody. For the age group 6 months through 17 years, Fluzone Intradermal provides no meaningful therapeutic benefit over licensed influenza vaccines. While there are no serious safety concerns for Fluzone Intradermal, considering the greater risk for local reactogenicity, it is not likely to be used in a substantial number of infants and children 6 months through 17 years of age.

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7. SAFETY

In two pivotal clinical trials (FID02 and FID31), a total of 3,496 adults 18 through 64 years of age received at least one dose of Fluzone Intradermal and were included in analyses of safety. A subset of 507 subjects received a dose of Fluzone Intradermal in two consecutive years. In supportive studies that evaluated the safety of Fluzone Intradermal at a higher dose (FID04, FID29, and FID21) in elderly persons ≥65 years, a total of 1,785 subjects received at least one dose of Fluzone Intradermal.

Fluzone Intradermal is associated with a notably higher incidence of some local injection site reactions, including Grade 3 reactions, compared with Fluzone administered

intramuscularly. In the largest clinical study (Study FID31), imbalances between the Fluzone Intradermal group and the Fluzone group were observed for erythema (76% vs. 13%, respectively), induration (58% vs. 10%, respectively), pruritus (47% vs. 9%, respectively), swelling (57% vs. 8%, respectively), and any Grade 3 solicited injection site reaction (15% vs. 3%, respectively) occurring in the period 0 through 7 days post-vaccination. Erythema >5 cm accounted for most Grade 3 solicited injection site reactions. The incidence of injection site pain, approximately 50%, was similar for the two groups. Most solicited injection site reactions had an onset within 3 days following vaccination and resolved by Day 7 following vaccination. Any solicited injection site reaction was present on Day 8 or later post-vaccination in 5.8% of subjects who received Fluzone Intradermal and 1.4% of subjects who received Fluzone. Erythema accounted for most of the local reactions present on Day 8 or later following Fluzone Intradermal. Local reactions following Fluzone Intradermal were self-limited and infrequently required medication or medical attention. Local reactions following Fluzone Intradermal generally were more frequently reported by females than males, with the greatest differences noted for pain (59.0% in females vs. 36.9% in males), pruritus (51.5% vs. 38.8%, respectively), and induration (61.9% vs. 52.2%, respectively). Among Fluzone recipients, gender differences in the occurrence of injection site reactions also were observed, but were less pronounced than among Fluzone Intradermal recipients, with the greatest difference observed for pain (58.4% in females vs. 45.7% in males). No notable and consistent imbalances between Fluzone Intradermal and Fluzone were observed in terms of solicited systemic adverse events or serious adverse events. In Study FID31, 3.9% of Fluzone Intradermal recipients and 2.6% of Fluzone recipients reported fever in the period 0 through 7 days post-vaccination; 0.4% of Fluzone Intradermal recipients and 0.4% of Fluzone recipients reported a serious adverse event in the period 0 through 28 days post-vaccination. In Study FID33, a revaccination study in adults 18 through 64 years of age who participated in Study FID31 the previous year, prior vaccination with Fluzone Intradermal appeared to be associated with a somewhat higher frequency of reported injection site erythema, swelling, and induration following either Fluzone Intradermal or Fluzone in Year 2.

Pharmacovigilance Plan

The pharmacovigilance plan was found to be adequate. The sponsor has designated adverse events of special interest (AESIs) that will be reported in expedited fashion, and all adverse events meeting the regulatory definition of "serious" will be reported as 15 day reports (regardless of whether labeled/expected). They will monitor AESIs as well as other potential risks based on post-marketing experience with Fluzone using routine signal detection and evaluation methods, and AESIs and potential risks (identified pre and post licensure) will be reported in Periodic Safety Update Reports (PSURs). Based on the reproductive-developmental toxicology data on Fluzone Intradermal provided in the supplement, pregnancy category B has been recommended for Fluzone Intradermal. CBER requested that the sponsor establish a Pregnancy Registry for Fluzone Intradermal as part of a comprehensive effort to collect more data on vaccines and pregnancy outcome. The sponsor agreed.

8. ADVISORY COMMITTEE MEETING

It was determined that review of the sBLA for Fluzone Intradermal by the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was not required because of CBER's experience with the currently licensed Fluzone and Fluzone High-Dose products, and because Fluzone Intradermal manufacturing is identical to the procedures used for the currently licensed Fluzone High-Dose product except for the final container. Furthermore, because 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, it was agreed that review of this sBLA by the VRBPAC was not necessary.

9. OTHER RELEVANT REGULATORY ISSUES

There are no other relevant regulatory issues of note.

10. LABELING

The proprietary name Fluzone Intradermal was approved by the Advertising and Promotional Labeling Branch. The carton and syringe labels were reviewed and found to be acceptable after several minor changes. The proposed package insert required only minor modifications. After negotiations with the sponsor, it was determined by the committee that the prescribing information for Fluzone Intradermal is acceptable.

11. RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT

There were two post-marketing commitments related to the approval of this supplement. In the first, the sponsor agreed to revise or change the current container closure integrity test (CCIT) method, and to validate the revised or different method with adequate sensitivity to demonstrate detection of a critical leak. In the second, the sponsor agreed to establish a Pregnancy Registry for Fluzone Intradermal.

The committee recommends approval of this sBLA.