

Title Page and General Information

BLA number: 125285

Related IND numbers: 11951

Reviewer name, division, and mail code:

Clinical Reviewer: Cynthia Nolletti, MD, CBER/OVRR/VCTB/Clinical Trials Branch, HFM 485.

Supervisory Reviewer: Lewis Schrager, MD, Branch Chief, HFM 475.

Draft Review Completed: August 4, 2009

Draft Final Review Completed: December 17, 2009

Final Review Completed: January 15, 2013

Original Submission Received by FDA: April 18, 2008

Complete Response #1 Received by FDA: April 28, 2009

Complete Response #2 Received by FDA: July 17, 2012

1.2 Product

1.2.1 Established Names: Influenza Vaccine, Recombinant Hemagglutinin

1.2.2 Proposed Trade Name: Flublok

1.2.3 Product Formulation:

The 2012-2013 vaccine will contain recombinant hemagglutinin (rHA) antigen from three influenza virus strains:

- 45µg rHA A/California/7/2009 (H1N1)
 - 45µg rHA A/Victoria/361/2011 (H3N2)
 - 45µg rHA B/Wisconsin/1/2010
- Total 135µg HA antigen per 0.5 mL dose.

Flublok contains the following excipients per 0.5mL dose:

- Sodium phosphate, 10-20 mM
- Sodium chloride, 150 mM
- Polysorbate 20 (Tween-20), 0.005%
- —b(4)-----

Flublok will be provided in single dose glass vials with rubber closures (stoppers), and should be stored in a refrigerator at 2°C to 8°C until use.

1.2.4 Biochemical Name, Structure

Purified Recombinant Influenza Hemagglutinin (derived from influenza A subtypes H1 and H3, and type B strains)

The recombinant antigens are full length, uncleaved glycoproteins with molecular weights of approximately 65,000 Daltons, and are considered to be the major antigenic components that induce a protective immune response. Full length hemagglutinin (HA) genes from the three influenza viruses are inserted into the plasmid baculovirus expression vector *Autographa californica* Nuclear Polyhedrosis Virus (AcNPV). The recombinant HA proteins are then expressed by baculovirus-infected expresSF+

(Lepidopteran) insect cells (*Spodoptera frugiperda*). The purified proteins are formulated in PBS without preservatives, antibiotics, or adjuvants.

1.3 Applicant: Protein Sciences Corporation (heretofore called “Applicant” or “PSC”)

1.4 Pharmacologic Class or Category: Vaccine

1.5 Proposed Indication: For active immunization of adults 18 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

1.6 Proposed Population(s): Adults 18 years of age or older.

1.7 Dosage Form and Route of Administration: 135µg influenza HA antigen (45µg per strain) per 0.5mL dose administered intramuscularly (IM).

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Glossary

ACIP = Advisory Committee on Immunization Practices
AE = adverse event
APLB = Advertising and Promotional Labeling Branch
BCA = bicinchoninic acid assay
BEVS = baculovirus expression vector system
BIMO = Bioresearch Monitoring
BLA = biologics license application
CBER = Center for Biologics Evaluation and Research
CCHMC = Cincinnati Children's Hospital Medical Center
CDC = Centers for Disease Control and Prevention
CFR = Code of Federal Regulations
CI = confidence interval
CMC = Chemistry, Manufacturing, and Controls
CR = Complete Response
CRF = case report forms
CRO = contract research organization
CSR = Complete Study Report
DCC = Document Control Center
DE = Division of Epidemiology
DMC = Data Monitoring Committee
DMID = Division of Microbiology and Infectious Diseases, NIAID, NIH
DVP = Division of Viral Products
EMA = European Medicines Agency
EOIS = end of influenza season
EU = European Union
FDA = Food and Drug Administration
GCP = Good Clinical Practice
GMT = geometric mean titer
GBS = Guillain Barre Syndrome
HA = hemagglutinin
HAI = hemagglutinin inhibition
ICH = International Conference on Harmonization
ILI = influenza-like illness
IM = intramuscular
IND = investigational new drug
IR = Information Request
IRB = Institutional Review Board
ISR = interim study report
LAIV = live attenuated influenza vaccine
LB = lower bound
LOD = limit of detection
MedDRA = Medical Dictionary for Regulatory Activities
NA = neuraminidase
NA = neutralizing antibody
N/A = not applicable

NCI = National Cancer Institute
NCT = National Clinical Trial
NIAID = National Institute for Allergy and Infectious Diseases
NIH = National Institutes of Health
NP = nasopharyngeal
NS/TS = nasal swab/throat swab
OBE = Office of Biostatistics and Epidemiology
ORS = Oculorespiratory Syndrome
OVR = Office of Vaccines Research and Review
PBO = placebo
PCR = polymerase chain reaction
PeRC = Pediatric Review Committee
PI = Package Insert
PMC = postmarketing commitment
PMH = past medical history
PMR = postmarketing requirement
PREA = Pediatric Research Equity Act
PSC = Protein Sciences Corporation
PT = preferred term
PVP = Pharmacovigilance Plan
QIV = quadrivalent influenza vaccine
rHA = recombinant hemagglutinin
RE = relative efficacy
RR = relative risk
RT = reverse transcriptase
SAE = serious adverse event
SAP = Statistical Analysis Plan
SCR = seroconversion rate
SDW = source document worksheet
SOC = system organ class
SRI = Southern Research Institute
SRID = serial radial immunodiffusion assay
STN = submission tracking number
TIV = trivalent influenza vaccine
UB = upper bound
URI = upper respiratory infection
VRBPAC = Vaccines and Related Biological Products Advisory Committee
VAERS = Vaccine Adverse Event Reporting System
VE = vaccine efficacy

3.0 Executive Summary

Flublok, the trivalent recombinant hemagglutinin influenza vaccine produced by Protein Sciences Corporation (PSC), without the use of eggs by a novel manufacturing process, is recommended by this clinical reviewer for approval in adults 18 through 49 years of age. This is a third cycle approval following issuance of two Complete Response (CR) letters due to a combination of clinical and manufacturing deficiencies. The second CR, submitted on July 17, 2012, satisfactorily addressed all outstanding issues. Approval is recommended based on the demonstration of effectiveness in prevention of culture-confirmed influenza illness in persons 18-49 years of age. Approval is also recommended based on an acceptable safety profile and the absence of clear safety signals, albeit in a relatively small database. Although no safety signal was identified from the studies submitted to this BLA, the Applicant has agreed to a postmarketing commitment (PMC) to conduct a Phase 4 observational safety study to further characterize the safety profile of Flublok and evaluate the potential for uncommon adverse events. Safety and immunogenicity studies in children 3 years to less than 18 years of age will be conducted as a postmarketing requirement (PMR) to fulfill the pediatric assessment required under the Pediatric Research Equity Act (PREA). In addition, the Applicant has agreed to establish a pregnancy registry as a PMC. Data submitted to the BLA were not found sufficient to recommend approval in persons 50 years of age and older. The Applicant will need to collect additional safety and effectiveness data to support licensure in this age group.

Flublok consists of three recombinant influenza hemagglutinin antigens derived from influenza virus A subtypes H1 and H3, and B type strains. The hemagglutinin (HA) genes from the three influenza viruses are inserted into a plasmid baculovirus expression vector system (BEVS) and expressed in *Spodoptera frugiperda* insect cells. The proposed indication is for the active immunization of adults 18 years and older against influenza disease caused by influenza subtypes A and type B contained in the vaccine. The proposed dosage in adults is 135µg [45µg per recombinant hemagglutinin (rHA) antigen] administered intramuscularly.

Data from four clinical trials comprising a total population of 3,231 adults 18 years and older were submitted to support licensure. Although data on vaccine effectiveness were collected in all four clinical trials, only one Phase 3 study of young healthy adults (PSC04) was adequately powered to evaluate vaccine efficacy (VE) in preventing virus culture-confirmed influenza illness based on pre-specified statistical criteria. PSC04 demonstrated that, in an influenza season characterized by a predominance of antigenically mismatched strains, the VE of Flublok against culture-confirmed influenza illness [not necessarily meeting the Centers for Disease Control and Prevention (CDC) case definition] due to any virus strain regardless of antigenic match was 44.8% with a lower bound of the 2-sided 95% confidence interval (LB 95% CI) of 24.4%. This was a post hoc exploratory analysis. A pre-specified exploratory analysis of protection against culture-confirmed CDC-defined influenza-like illness (ILI) due to any virus strain demonstrated a VE of 44.6% (95% CI 18.8, 62.6). Although the sample size was small in the earlier phase study PSC01, the estimates of VE for young healthy adults also

suggested a trend towards protective efficacy. Studies PSC06 and PSC03 were active-control trials in older adults (ages 50-64 years and ≥ 65 years, respectively). Mismatched strains predominated during these studies, and in each study the numbers of culture-confirmed influenza cases were too small to draw meaningful conclusions regarding the relative risk of influenza among older adult recipients of Flublok relative to the licensed comparator vaccines.

Flublok failed to meet the pre-specified clinical efficacy criteria for the primary endpoint of influenza illness caused by virus strains antigenically similar (“matched”) to those in the vaccine. However, the trial was conducted during an influenza season that was characterized by a predominance of antigenically mismatched strains, and few cases of influenza due to vaccine-matched strains were available for evaluation. It is reasonable to expect that Flublok’s efficacy against matched strains would be at least as good as the VE of 44.8% (LB 24.4%) demonstrated against predominantly mismatched strains. In fact, the point estimate for the primary clinical endpoint of prevention of CDC-defined ILI in study PSC04 was 75.4%. However, cases of CDC-ILI were few (Flublok = 1, placebo = 4) and confidence intervals (CIs) on the point estimate were wide and included zero. While the efficacy data are adequate to support licensure in adults 18 through 49 years of age, an additional clinical endpoint study will be recommended to support extension of the approved use of Flublok to older populations (persons 50-64 years and ≥ 65 years of age).

The total immunogenicity population for Flublok was comprised of 1,328 subjects from two placebo-controlled and two active-controlled trials that enrolled both young healthy adults and older adults. Thirty-two percent of these subjects were 65 years of age and older. The administration of Flublok at 135 μ g total rHA elicited an immune response that exceeded pre-specified hemagglutinin inhibition (HAI) titer endpoints for the H1 and H3 strains in all four studies representing different age groups and populations, and reflected manufacturing over three influenza seasons. In contrast, the B strain failed to meet criteria for immune responses in three of the four studies and failed a non-inferiority comparison to Fluzone in one of two studies (in adults 65 years of age and older). The B strain met both endpoints in the largest Phase 3 study (PSC04) in young healthy adults and demonstrated non-inferiority to Fluzone in adults 50 to 64 years of age. Flublok’s weaker performance against the B strain is similar to other currently licensed influenza vaccines that have also elicited low immune responses to the B strain. However, concerns over the HAI assay including the fact that HAI titers obtained when BEVS-derived antigens are used in the assay are substantially higher than when egg-derived antigens are used contribute to the difficulty in interpreting immunogenicity data and bridging immunogenicity data from the older adult studies to the clinical efficacy data in adults 18 through 49 years of age. Additionally, because PSC04 did not meet the primary endpoint of absolute VE against matched strains, the review team determined that additional immunogenicity data will not be sufficient and a clinical endpoint study will be needed to confirm vaccine effectiveness in the older age groups (50-64 years and 65 years and older).

The review team also agreed that additional data to support the HAI assay validation and to assess the comparability of BEVS-derived versus egg-derived antigens used in the assay would be needed to facilitate the interpretation of data collected in future immunogenicity studies, including studies to support extension of the age indication to the pediatric population.

The safety database for Flublok at 135µg total rHA consisted of 3,233 subjects 18 years of age and older. There was no imbalance of adverse events overall. No unusual trends, patterns or safety signals were observed. The type and frequency of adverse events experienced by Flublok subjects were similar to those reported for other trivalent influenza vaccines (TIVs).

The safety data for Flublok are limited by the relatively small size of the database, especially for a novel vaccine, particularly in persons 50 years of age and older (n=736), and by a loss to follow-up rate of 11% by the end of study PSC04. However, the discontinuation rate for PSC04 at Day 28, by which time most common adverse reactions, including hypersensitivity events, would have been captured, was 4%. The data, though limited, are adequate to observe adverse events that occur with a frequency of approximately 1 in 1000 vaccinees. There was one non-serious hypersensitivity event (lip and tongue swelling) in an individual with a history of atopy that appeared definitely related to Flublok. A second event, assessed as serious and one that may have represented an adverse reaction due to Flublok, was a case of pleuropericarditis. An extensive evaluation of the pleuropericarditis case did not reveal an infectious etiology but failed to adequately exclude enteroviruses. The causality of this event therefore remains unknown. Overall, the safety data are adequate to support licensure in adults 18 through 49 years of age. However, because Flublok is a vaccine manufactured by a novel process, the safety database should be enhanced by post-licensure studies in this age group to further evaluate the risk of less common adverse events including hypersensitivity events and pleuropericarditis.

The safety database in older adults from studies PSC03 and PSC06 was relatively small and included fewer subjects than the minimum number originally recommended by FDA during clinical development of this product. Therefore, traditional approval in adults 50 to 64 of age and 65 years and older is not recommended at this time because of insufficient safety, immunogenicity, and vaccine efficacy data.

Flublok was the subject of a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting held on November 19, 2009. The committee voted 9 to 2 that the data supported Flublok effectiveness in adults 18 through 49 years of age, but voted that the data did not support effectiveness in adults 50 years and older. The committee was divided, voting 5 to 6 that the safety data did not support licensure in adults 18 years of age and older. This was due primarily to the relatively small size of the safety database for a novel vaccine. Accordingly, a postmarketing safety study will be conducted in adults 18-49 years of age and additional safety and effectiveness data will be required and reviewed before the indication is extended to persons 50 years and older.

PSC and FDA agree that the following additional clinical studies will be conducted postmarketing: 1) a large observational safety study in persons 18 through 49 years of age; 2) safety, immunogenicity and clinical efficacy studies in persons 50 years of age and older; 3) safety and immunogenicity studies in children and adolescents 3 through 17 years of age; and 4) a pregnancy registry. To address FDA concerns over the HAI assay, additional data to support the HAI assay validation and the comparability of BEVS-derived and egg-derived antigens used in the assay will be submitted when future immunogenicity studies are conducted.

4.0 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC)

Vaccine potency was measured by the serial radial immunodiffusion assay (SRID), the same method used to assess potency of licensed TIVs. Each monovalent bulk lot was formulated with a target of 45µg of rHA antigen per dose measured by SRID. Total protein, as measured by the bicinchoninic acid (BCA) assay, was also specified in the formulation of the final drug product. ---b(4)-----

Please see the reviews by Maryna Eickelberger, Matthew Sandbulte, Arifa Khan and Rajesh Gupta. The primary concerns have related to purity, potency, stability, lot consistency, and -b(4)-- -----

The expiry period, based on stability data, is 16 weeks.

4.2 Reproductive/developmental Toxicity

Dr. Marion Gruber, the reproductive toxicology reviewer, reviewed the Final Study Report for the reproductive safety and immunogenicity studies of Flublok in rats. Dr. Gruber concluded that, under the conditions of the study, Flublok does not appear to affect embryo-fetal pre- and post-natal development and does not appear to exert teratogenic effects. Dr. Gruber recommended that Flublok receive a pregnancy category B.

4.3 Statistics

The analyses by Dr. Barbara Krasnicka, the statistical reviewer, were similar to the Applicant's report. Dr. Krasnicka identified unusual variability in geometric mean titer (GMT) responses and ratios across the studies both before and after adjusting for HAI assays, baseline HAI titers and lots. This was true primarily for H3 in PSC04, and in studies PSC03 and PSC06. It was true for both subjects and assay runs within and between lots and across studies. The statistical reviewer requested information regarding this variability in the August 29, 2008 CR letter. In their April 28, 2009 CR, the Applicant stated that the variability in GMTs may be related to differences in age, previous exposure and vaccination, and to virologic differences in antigenicity of the

vaccine strains. PSC also demonstrated that GMTs in the Fluzone control groups showed similar variability. The statistical review of the April 28, 2009 CR concluded that the assay variability did not significantly affect the immunogenicity conclusions of these studies. However, additional concerns over the HAI assay subsequently emerged. Please see HAI Assay Validation, Section 4.4, and the updated statistical review by Dr. Krasnicka for further discussion of this issue.

The statistical review also considered the high dropout rate in study PSC04 and missing serologic data to be deficiencies, and noted that primary endpoints relating to lot consistency, immunogenicity of the B strain, and vaccine efficacy were missed.

Reviewer comment: These issues were resolved to the review team's satisfaction and are addressed throughout the clinical review, particularly in Sections 8.1.1.2., 9, 10, and 12.

4.4 HAI Assay Validation

Please see the review by Dr. Lev Sirota and references to the HAI assay in the Overview of Efficacy, Sections 9, for a discussion of the approaches taken to the HAI assay validation.

CBER review team's understanding of the HAI assay evolved since this BLA was submitted in April 2008. The Applicant was told in the pre-BLA meeting (September 21, 2007) that BEVS-derived antigens could be used in the assay. However, because of the unusual variability in GMTs noted by Dr. Krasnicka during the review process, Dr. Lev Sirota (Statistical Assay Reviewer) and Dr. Maryna Eichelberger Division of Viral Products (DVP) were also asked to re-evaluate the HAI assay validation for inherent problems with the assay. The statistical reviewers felt that the validation including the comparability study evaluating HAI titers using both BEVS- and egg-derived antigens could have been more rigorous. Although, in December 2009, the statistical review team ultimately determined that the variability in the GMTs did not influence the comparison of treatment groups or the overall interpretation of study results, data subsequently submitted by PSC from the Phase 1 clinical study of its recombinant H5 (rH5) pandemic influenza vaccine, PanBlok (IND --b(4)--), on August 2, 2011 resurrected concerns relating to the HAI assay validation and the use of BEVS-derived antigens. An Information Request (IR) regarding the study results and the HAI assay was sent to the Applicant on September 30, 2011. On March 16, 2012, the Applicant responded to the IR and informed FDA that they had decided to have a different laboratory perform the HAI titers. GMTs, seroconversion rates (SCRs) and proportions of subjects with postvaccination HAI titers $\geq 1:40$ from the new laboratory, --b(4)-- ----- were more consistent with results from a population that was immunologically naïve to the pandemic strain than were the original HAI results from the Cincinnati Children's Hospital Medical Center (CCHMC) laboratory.

In addition to concerns regarding the CCHMC HAI assay that was also used to perform HAI titers for the original Flublok BLA studies, interpretation of HAI titers using BEVS-derived antigens is associated with some uncertainty. Because the use of BEVS-derived

antigens in the HAI assay yields higher HAI titers as compared to egg-derived antigens, it is not clear that a post-vaccination HAI titer of 1:40 obtained using BEVS-derived antigens is reasonably predictive of protection as is generally accepted when egg-derived antigens are used. The higher titers expected with the use of BEVS-derived antigens may have implications for the immunologic non-inferiority criteria that have been used to evaluate effectiveness in the older age groups, or the criteria used to bridge immune response data from other age groups to absolute vaccine efficacy data in the 18-49 year old age group.

The issues with the HAI assay and their impact on approval recommendations will be discussed further in the Overview of Efficacy, Section 9, and Conclusions Overall, Section 12.

4.5 Facilities Review

Please see the review by Deborah Trout. Outstanding issues at the time of the August 29, 2008 CR included failure of lots to meet specifications and lots of H1N1 being out of trend for the specified antigen content as measured by SRID. These issues have been adequately addressed.

4.6 Bioresearch Monitoring (BIMO)

Three clinical study sites were inspected by the BIMO team:

- Cincinnati, OH Site # 22 N= Flublok 100 - 100 Placebo
- Austin, TX Site #05 N= Flublok 127 - 126 Placebo
- Beverly Hills, CA Site # 13 N= Flublok 155 - 140 Placebo

Among other considerations such as study population and geographic distribution, Site 5 (PSC03) was selected for inspection because of a break in the study blind, and Site 13 (PSC04) was selected because it had deviated from the randomization scheme (details follow in the clinical review). The BIMO inspection did not identify any investigator deficiencies that would preclude approval of the product. Please see the review by Robert Wesley for further discussion and comments.

5.0 Clinical and Regulatory Background

5.1 Disease or Health-Related Conditions Studied and Available Interventions

Influenza continues to be one of the greatest infectious causes of death in the United States and throughout the world, with mortality rates of 17,000 to 51,000 persons (mean 36,000) in the U.S. and 250,000 to 500,000 persons worldwide each year. It is responsible for more deaths in the U.S. than all other vaccine-preventable diseases combined. In the U.S., mortality increased from 1990 to 1999, and annual influenza-associated hospitalizations ranged from 55,000 to 431,000.

Influenza is caused by RNA viruses of the family Orthomyxoviridae. Two types, influenza A and influenza B, cause the vast majority of human disease. Influenza A is further categorized into subtypes on the basis of two principal surface antigens, hemagglutinin (HA) and neuraminidase (NA), which comprise the viral glycoprotein coat. There are multiple subtypes of Influenza A based on combinations of 16 variants of

HA and 9 variants of NA, but only the subtypes H1N1, H2N2, and H3N2 appear to circulate in humans. In addition to humans, Influenza A has been isolated from non-human species including birds, horses, and swine. Influenza B is comprised of single HA and NA subtypes, and is known to occur only in humans. Antibodies to the surface antigens are subtype and strain-specific, and confer protection against future infection with identical strains, but not against another type or subtype.

Since 1977, influenza A subtypes H1N1 and H3N2 and influenza B have circulated globally. Seasonal epidemics generally occur during the winter months and are caused by antigenic drift, new antigenic variants or viral strains that result from point mutations in the viral genome that occur during replication. Antigenic variants or strain changes occur each year necessitating yearly change in the formulation of the TIV for optimal protection. Neutralizing antibody (NA) against HA is the primary immune defense against infection with influenza. Although there is no established absolute immune correlate of protection, studies have suggested that HAI titers of 1:32 to 1:40 correlate with protection against illness. This strain-specific immune response appears to predict a clinical endpoint of efficacy with reasonable certainty. Previous experience with inactivated TIVs suggests that HAI titers might be used as a surrogate endpoint.

The primary mode of controlling influenza disease remains immunoprophylaxis. In view of the potential for serious and life-threatening influenza-related disease, the Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) has, in recent years, broadened their recommendations for persons in whom annual influenza vaccination is recommended to include all persons 6 months of age and older.

Licensed influenza vaccines available in the United States include: trivalent and quadrivalent inactivated (TIV and QIV) and live-attenuated influenza vaccines (LAIV). These vaccines are grown either in egg or cell culture. LAIV is currently approved for use only in healthy non-pregnant persons 2 to 49 years of age. When vaccine and circulating viruses are antigenically well-matched, vaccination with TIV has been estimated to be approximately 70-90% effective in preventing influenza illness among young healthy adults < 65 years of age. These estimates are limited by a relative lack of randomized placebo-controlled trials. Effectiveness is lower among persons with underlying illnesses, those \geq 65 years of age, or when there is a poor antigenic match between vaccine and circulating influenza virus strains.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

There are now seven licensed TIVs in the United States: Afluria (CSL), Agriflu (Novartis), Fluarix (GSK), Flucelvax (Novartis), FluLaval (GSK, formerly ID Biomedical), Fluvirin (Novartis, formerly Chiron), and Fluzone (sanofi pasteur). These are approved for use in adults. In addition, Afluria is approved for use in persons 5 years of age and older, Fluarix for persons 3 years of age and older, Fluvirin for persons 4 years of age and older, and Fluzone persons 6 months of age and older. FluMist (MedImmune) is the only licensed LAIV in the U.S., and is currently approved for use only in healthy

persons aged 2 to 49 years. On February 29, 2012, FluMist Quadrivalent became the first licensed influenza vaccine to contain two B strains. With the exception of Flucelvax, all of these licensed products are manufactured in hen eggs.

Production of egg-based TIVs is a lengthy and unpredictable process, subject to time constraints, the need for adaptation of virus to growth in eggs, potential problems with the hen flock and subsequent shortages of vaccine. A shorter manufacturing time would be advantageous, particularly in the event of a pandemic such as the 2009 H1N1 pandemic. Cell-culture manufacturing techniques may shorten production time and offer the potential for rapid scale up in production. On November 20, 2012, Flucelvax became the first cell culture-based influenza vaccine to be produced in the U.S.

Flublok is a novel trivalent influenza vaccine consisting of three recombinant influenza HA antigens derived from influenza A subtypes H1 and H3 and type B strains. The HA genes from the three virus strains are inserted into a baculovirus expression vector, and grown in *Spodoptera frugiperda* insect cells. There are no U.S. licensed influenza vaccines that are manufactured in *Spodoptera frugiperda* (Sf) or other insect cells or that use baculovirus expression vector recombinant technology. However, baculovirus-insect cell-based technology has been widely used in academia and industry to produce recombinant proteins for research and commercial applications.

Cervarix, a recombinant vaccine for prevention of human papilloma virus infection in women, is also expressed using a baculovirus vector, but in a different insect cell line, *Trichoplusia ni*. Cervarix is licensed in the U.S. other countries.

Flublok has potential advantages over traditional egg-grown TIVs. The time required to clone and manufacture Flublok is approximately 2 months, and the production process can be scaled up to produce large quantities of antigen. A shorter manufacturing time may allow selection of HA antigens more closely related to real time circulating influenza strains, and theoretical advantages during a pandemic are obvious. Another potential advantage to the non-egg based manufacturing process is the ability to use vaccines like Flublok in persons with severe egg allergies.

5.3 Previous Human Experience with the Product Including Foreign Experience

A total of fourteen clinical human trials have been conducted with PSC's rHA vaccines as of May 2008. Nine trials have been conducted under three INDs held by NIAID/NIH. Of these, 534 subjects received mono- or bivalent vaccine. The remaining 321 subjects were vaccinated with trivalent formulations. Of these 321 subjects, 300 elderly subjects received rHA vaccine in DMID 03-119 and 21 patients with B-cell lymphoma received rHA in DMID 04-036. A total of 7 different rHAs were utilized in these nine trials in total doses ranging from 10µg to 405µg. These nine studies were not formally submitted to the BLA in support of the initial indication for Flublok.

5.4 Regulatory Background Information

July 1, 2006: Submission of PSC03 was originally intended to support accelerated approval on the basis of immune response and safety. Study PSC03, however, did not

meet the planned enrollment. CBER provided guidance to the Applicant that a new BLA submission should contain a study adequately powered for successful immune response endpoints as outlined in the CBER Guidance Document and should contain a total safety database appropriate for a new vaccine manufacturing process.

June 8, 2007: PSC submitted two additional Phase 3 study protocols, PSC04 and PSC06, as IND 11951 Amendment 39. The studies addressed the immune response endpoint for consideration of accelerated approval and provided additional subjects receiving Flu Blok for the safety database.

Reviewer comment: The statistical reviewer recommended a larger sample size to evaluate the proposed non-inferiority endpoints in Study PSC06. However, the Applicant chose not to increase the sample size for this study.

September 21, 2007 – Pre-BLA Meeting. Because the database lock, final analysis, and write-up of studies PSC04 and PSC06 were not expected to be completed until approximately August 2008, FDA and PSC agreed that PSC would submit the final clinical study reports for studies PSC04 and PSC06 containing the 6-month SAE and clinical efficacy data in a BLA supplement within 6 months of accelerated approval.

December 6, 2007 – Type C Meeting to discuss outstanding CMC issues.

April 18, 2008 – PSC submitted BLA STN #125285 requesting accelerated approval for Flublok. For studies PSC04 and PSC06, the submission contained Interim Study Reports (ISRs) with safety and immunogenicity data through Day 28.

August 29, 2008 – A CR letter was issued by FDA to PSC requesting additional information regarding CMC, Clinical and Statistical issues. Please see the CR letter for details. The major clinical deficiencies included: 59 subjects unaccounted for in the immunogenicity subset of PSC04; absence of an immunogenicity placebo control in the pivotal study (PSC04); failure of the B strain to meet pre-specified immune response and non-inferiority endpoints; failure of the H3N2 strain to meet lot consistency endpoints; unexplained variability in GMTs for all strains by lot and assay; general medical history data for subjects in PSC04 not submitted; a break in the blind at one study site; and discrepancies between the Applicant's study report and the electronic datasets.

April 28, 2009 – PSC responded to the August 2008 CR providing CSRs containing additional clinical efficacy and 6-month safety data from PSC04 and PSC06, and requested traditional approval for Flublok.

November 19, 2009 – Advisory Committee Meeting. Because Flublok represents a novel antigen produced by a new manufacturing process, this product was presented to the VRBPAC. The committee voted 9 to 2 that the data supported the effectiveness in adults 18 through 49 years of age, but voted that the data did not support effectiveness in adults 50 years of age and older. The committee was divided on whether the data supported

safety in persons 18 years of age and older. Please see summary of key points in VRBPAC Recommendations, Section 12.1, of this review.

January 11, 2010 – A second CR letter for Flublok STN 125285 was issued to PSC. A clinical reviewer recommendation that additional safety and efficacy studies be required both pre- and post-licensure, and draft clinical comments for the CR letter were communicated to supervisors in December 2009 (emails 12/2/2009 and 12/7/2009). A statistical reviewer recommendation to repeat the HAI assay validation was also communicated. However, because Flublok’s manufacturing deficiencies, including the presence of ---(b)(4)--- in the monovalent bulk lot, were considered so extensive, upper management determined that the CR items should address only the CMC deficiencies and that additional clinical studies with the product would not be recommended at that time.

July 17, 2012 – PSC submitted their response to the second CR, STN 125285/0.57 (DATS login ID 439161). The new Action Due date became January 16, 2013. The Applicant adequately addressed issues relating to potency, purity, and lot consistency. Please see the CMC reviews for complete discussions of these issues.

August 1, 2012 – FDA informed PSC that approval would be considered only for persons 18 to 49 years of age in this review cycle. This was followed by a telecon with the PSC on August 8, 2012 during which FDA stated its intention to grant traditional or full approval in persons 18-49 years of age provided that the CMC data were acceptable. The Applicant was informed that additional safety data would be requested in all age groups, that additional safety and effectiveness data would be required prior to approval in persons 50 years of age and older. Discussion of the details of additional studies to be considered was deferred to a follow-up meeting with the Applicant held on August 30, 2012.

Details of the post-marketing negotiations are outlined in the “Postmarketing Negotiations” section of this addendum.

6.0 Clinical Data Sources, Review Strategy, and Data Integrity

6.1 Material Reviewed

6.1.1 BLA Volumes

The clinical review of BLA submission STN125285/0 focused on the following modules, volumes and amendments:

- Module 1 Volume 1: Administrative information, PVP, labeling.
- Module 2 Volume 1: Overviews of clinical efficacy, safety, and non-clinical data.
- Module 5 Volumes 1-32: These included the final protocols and interim clinical study reports for each of the four studies submitted to the BLA. Line listings, sample diary cards, telephone scripts, case report forms (CRFs), informed consent forms were reviewed.

- STN 125285/0.2: Amendment containing the final protocols and Statistical Analysis Plans (SAPs) for each of the four studies submitted to the BLA in one volume.
- STN 125285/0.4 (June 13, 2008) – Response to IR.
- STN 125285/0.5 (June 26, 2008) – IR re: disposition of subjects.
- STN 125285/0.8 (July 25, 2008) – Response to IR.
- STN 125285/0.12 (April 8, 2009) – Partial CR (Clinical and Statistical).
- STN 125285/0.13 (April 28, 2009) – Complete Response including final study reports and clinical efficacy data from studies PSC04 and PSC06.
- STN 125285/0.17 (July 15, 2009) – Response to June 19, 2009 IR.
- STN 125285/0.18 (July 17, 2009) – Response to June 19, 2009 IR, Pediatric Plan.
- STN 125285/0.20 (August 31, 2009) – response to August 14, 2009 Statistical IR.
- IND 11951/0.53 – Briefing Document for Type C Meeting Request. Path forward for persons 50 years of age and older.
- STN 125285/0.58 – (dated August 9, 2012; received by CBER/DCC on August 16, 2012). Updated Package Insert.
- STN 125285/0.60 – (dated August 31, 2012; received by CBER/DCC on September 4, 2012). Updated Pediatric Plan.
- STN 125285/0.63 – Received September 28, 2012. Response to September 9, 2012 IR requesting sub-analyses of safety, immunogenicity and vaccine efficacy according to gender, race and ethnicity.
- STN 125285/0.61 – (dated September 13, 2012). Revised Pediatric Plan.
- STN 125285/0.62 – Received by e-mail on September 21, 2012; by DCC on October 3, 2012. “Proposal for Management of Pregnancy Registry”.
- STN 125285/0.68 – (received by email Oct 22, 2012) Response to October 5th and 19th, 2012 IRs requesting that CIs be included in the data submitted in STN 125285/0.63, gender and racial/ethnicity sub-analyses (Clinical IR, October 5th) and questions regarding the pregnancy registry (OBE/DE IR, October 19th).
- STN 125285/0.66 – Response to September 28, 2012 IR, primarily CMC and a request from OBE/DE for an update to the proposed Phase 4 study outlined in the PVP. The response also outlined plans for the proposed studies in persons 50 years and older.
- IND 11951 Amendment 65. Submitted to DCC on November 13, 2012. Proposed protocols for the safety and vaccine efficacy studies in persons 50 years of age and older.
- STN 125285/0.70 – Received by e-mail on November 28, 2012; submitted to DCC on December 5, 2012. Revised labeling and Patient Information Sheet.
- STN 125285/0.74 – Received by e-mail on December 17, 2012. Revised labeling and response to FDA PMR and PMC December 13, 2012 IR.
- STN 125285/0.76 – Received by e-mail on December 21, 2012. Revised labeling.
- STN 125285/0.79 – Received by e-mail on December 9, 2012. Revised PMC and PMR commitment letter.

6.1.2 Literature

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6.1.3 Post-Marketing Experience

Flublok is not licensed in any country. Therefore, there is no postmarketing experience.

6.2 Clinical Studies

Clinical studies submitted to and reviewed for BLA 125285 can be found in Table 1.

Table 1 Clinical Studies Submitted to and Reviewed for BLA 125285

Study/ Season	Phase	n*	Age Group (years)	Strain/Dose	Control n
PSC01 2004-2005	2	153**	18-49	45µg A/New Caledonia/20/1999 (H1N1) 45µg A/Wyoming/3/03 (H3N2) 45µg B/Jiangsu/10/03	Saline 154
PSC03 2006-2007	3	436	≥65	45µg A/New Caledonia/20/1999 (H1N1) 45µg A/Wisconsin/67/2005 (H3N2) 45µg B/Ohio/1/2005	Fluzone 433
PSC04 2007-2008	3	2344	18-49	45µg A/Solomon Islands/3/2006/ (H1N1) 45µg A/Wisconsin/67/2005 (H3N2) 45µg B/Malaysia/2506/2004	Saline 2304
PSC06 2007-2008	3	300	50-64	45µg A/Solomon Islands/3/2006/ (H1N1) 45µg A/Wisconsin/67/2005 (H3N2) 45µg B/Malaysia/2506/2004	Fluzone 302
Total Database ≥ 18 yr	2 and 3	3233	≥18	n/a	319
PSC02***	1/2	97	6 to 59 Months	45µg A/New Caledonia/20/1999 (H1N1) 45µg A/Wisconsin/67/2005 (H3N2) 45µg B/Ohio/1/2005	Fluzone N=59

*n=number of subjects vaccinated with study vaccine

**Study PSC01 also included an additional group of subjects (n=151) who received 75µg total rHA (15µg H1 and B and 45µg of H3)

***PSC02 is included only as supportive information to the BLA. Half dose used in subjects 6 to 35 months.

The National Clinical Trial (NCT) numbers for these trials are as follows: PSC01=NCT00328107; PCS03=NCT00395174; PSC04=NCT00539981; PSC06=NCT00539864; PSC02=NCT00336453

Data from four clinical trials conducted under BB-IND 11951 were submitted by the Applicant in support of approval. Three of these were Phase 3 trials. The total immunogenicity population of 1328 subjects from two placebo-controlled and two active-controlled trials was comprised of both young healthy adults and older adults. Fifty-five percent of the immunogenicity database was 50 years of age and older, and 32% of subjects were 65 years of age and older. The total safety population for Flublok 135µg consisted of 3233 subjects 18 to over 65 years of age. Twenty-three percent of subjects were ≥ 50 years of age, and 13% were ≥ 65 years of age. The safety populations were also used as the denominators for the clinical endpoint analyses.

PSC01 (2004-2005, NCT00328107) was a Phase 2 randomized, modified double-blind, placebo-controlled, dose finding, safety, immunogenicity, and efficacy study of 458 healthy adults aged 18 to 49 years conducted at three centers in the U.S. Subjects were randomized 1:1:1 to receive a single dose of rHA 135µg (45µg per strain) vs. rHA 75 µg (45µg H3N2, 15 µg H1N1, 15µg B strain) vs. saline placebo. The Flublok 135µg dose was more immunogenic than the 75µg dose, and was, therefore, selected for further clinical development.

PSC03 (2006-2007, NCT00395174) was a Phase 3 randomized, modified double-blind, active-controlled study of 869 medically stable adults 65 years and over, conducted in the U.S. to evaluate the safety, immunogenicity and reactogenicity of Flublok compared to Fluzone. Protective efficacy was a secondary endpoint.

PSC04 (2007-2008, NCT00539981) was a Phase 3 randomized, double-blind, placebo-controlled clinical endpoint study in 4648 healthy adults aged 18 to 49 years conducted in the U.S. to assess safety and clinical efficacy. An immunogenicity subset of 391 Flublok and 127 Placebo recipients was used to evaluate immunogenicity and lot-to-lot consistency.

PSC06 (2007-2008, NCT00539864) was a Phase 3 randomized, double-blind, active-control non-inferiority study of 600 medically stable adults 50 to 64 years of age conducted in the U.S. The study evaluated safety, immunogenicity, and clinical efficacy. The regulatory intent of this study was to increase the safety database in an older adult population.

PSC02 (2006-2007, NCT00336453) was a randomized, double-blind Phase 1-2 multi-center dose-finding trial of Flublok in children 6 to 59 months of age submitted only to support a request for deferral of pediatric studies. The study objectives were to evaluate safety and immunogenicity and to determine the optimal dose and regimen of Flublok in two age groups: 6 to 35 months and 36 to 59 months.

6.3 Review Strategy

One Phase 2 and three Phase 3 studies were submitted to the BLA for review. Safety, immunogenicity and clinical efficacy data from the clinical study reports, line listings and electronic datasets were reviewed and compared. SAS datasets were evaluated using a JMP software program. Rates of adverse events (AEs) were calculated from the datasets and compared with the Applicant's report. In addition to providing case narratives and paper versions of CRFs for all SAEs, the Applicant was asked to and provided copies of the electronic CRFs and case narratives for selected SAEs, severe AEs, AEs of special interest, and pregnancies for review.

The study design across clinical studies is presented in Table 2.

Table 2 Study Design across Clinical Studies

Study/ Date	Phase	Age	N ¹	n ²	Random- Ization	Blind	Control	Sites (all US)
PSC01 2004-2005	2	18-49	153	150	1:1:1	MDB	Placebo	3
PSC03 2006-2007	3	≥65	436	431	1:1	MDB	Active	6
PSC04 2007-2008	3	18-49	2344	448	1:1	MDB	Placebo§	24
PSC06 2007-2008	3	50-64	300	299	1:1	MDB	Active	6
Total	n/a	≥18	3233	1328	n/a	n/a	n/a	39

N¹=evaluable population for clinical efficacy and safety analyses Flublok group

n²=evaluable population for immunogenicity Flublok group

MDB = modified double-blind. All subjects, site staff and laboratory personnel involved in efficacy evaluations were blinded except for the person administering the vaccine.

§Placebo control for safety and culture-confirmation. Originally no control for immunogenicity subset. Placebo group randomly selected post hoc.

All four trials were prospective randomized modified double-blind well-controlled multicenter studies. One difference between PSC04 and the other studies was that, for the immunogenicity subset, subjects in the placebo group had blood drawn for serologies, but the samples were not processed. Thus, a limitation of the study design in PSC04 was that there was a placebo control for safety and for the culture confirmation study, but not for the lot-to-lot consistency/immunogenicity subset. The Applicant agreed to an FDA request to perform a post hoc immunogenicity analysis on a randomly selected subset of subjects from the placebo group.

6.4 Good Clinical Practice (GCP) and Data Integrity

The four studies submitted to the BLA were conducted in the U.S. under BB-IND 11951. The studies were conducted in accordance with applicable regulatory requirements from the USA Code of Federal Regulations (CFR) guidelines on GCP. A BIMO assessment of field investigations of the clinical sites suggested that the data had good integrity. Please see Section 4.6 of this review and Robert Wesley's BIMO review for further discussion.

6.5 Financial Disclosures

Manon M.J. Cox, Chief Operating Officer of PSC, certified that none of the participating clinical investigators had any financial arrangements or interests related to the study product to disclose. The multicenter studies make it unlikely that any one investigator could influence the immune response, efficacy, or safety results of the studies submitted to the BLA.

7.0 Human Pharmacology

Exposure to influenza elicits a humoral immune response characterized by the development of antibodies to the major structural surface glycoproteins HA and NA. Neutralizing antibodies against HA are considered the primary protective response to infection with influenza. Although there is no absolute correlation, serum HAI titers of

1:32 to 1:40 or greater have been associated with protection against illness. Higher levels of antibody may be required for protection in older adults.

Protection is primarily strain specific. Antibody against one influenza virus type or subtype confers limited or no protection against another. Depending on the degree of antigenic drift, antibody to one strain may or may not protect against an antigenic variant within the same type or subtype. Development of antigenic variants through antigenic drift in the HA and/or NA glycoproteins each year or every few years is the immunologic basis for seasonal epidemics. The VRBPAC usually recommends a change in one or more of the three influenza vaccine antigenic strains each year for optimal protection.

8.0 Clinical Studies

The clinical studies of Flublok conducted under BB-IND 11951 are listed in Table 1. In addition, data from Study PSC02 is included only to provide supportive information to the BLA.

Clinical Studies of rHA vaccines conducted under INDs held by NIH/NIAID and used to support the safety database in the BLA (SAE narratives only) are listed below:

- NIH 93-028 (93A) (BB-IND 5305)
- NIH 94-004A (94A) (BB-IND 5305)
- NIH 94-004B (94B) (BB-IND 5303)
- NIH 94-004C (94C) (BB-IND 5305)
- NIH 94-004D (94D) (BB-IND 5305)
- NIH 98-001 (BB-IND 7507)
- NIH 98-027 (BB-IND 7507)
- DMID 03-119 (BB-IND 11244)
- DMID 04-036 (BB-IND 11244)

Effectiveness assessments

The immunogenicity endpoints for Flublok were assessed by using the HAI assay. Results were submitted to the original BLA in April 2008. The FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines: May 2007 has indicated that, for the purposes of accelerated approval of trivalent inactivated influenza vaccines, the HAI antibody response may be an acceptable surrogate marker of activity that is reasonably likely to predict clinical benefit. The endpoints and criteria for success are summarized below:

Immune Response Endpoints:

- Seroconversion rate: defined as the proportion of subjects with a:
 - Pre-vaccination HAI titer < 1:10 and a post-vaccination titer \geq 1:40, or
 - Pre-vaccination HAI titer \geq 1:10 and a minimum 4-fold rise in post-vaccination titer.
- Proportion of Subjects Achieving a post-vaccination HAI Titer \geq 1:40 (% \geq 1:40)

FDA Criteria for success:

For adults <65 years of age:

- The lower bound of the two-sided 95% CI for the proportion of subjects achieving a four-fold increase in HAI antibody titer to a minimum of 1:40 (SCR) should meet or exceed 40%.
- The lower bound of the two-sided 95% CI for the proportion of subjects achieving an HAI antibody titer $\geq 1:40$ should meet or exceed 70%.

For adults ≥ 65 years of age:

- The lower bound of the two-sided 95% CI for the proportion of subjects achieving a four-fold increase in HAI antibody titer to a minimum of 1:40 should meet or exceed 30%.
- The lower bound of the two-sided 95% CI for the proportion of subjects achieving an HAI antibody titer $\geq 1:40$ should meet or exceed 60%.

Reviewer comment: The Flublok BLA was initially submitted under accelerated approval regulations. The FDA Guidance criteria for accelerated approval are no longer relevant for the young adult population 18-49 years of age because Flublok will be approved on the basis of clinical efficacy.

Clinical Efficacy

- For the clinical efficacy endpoint, absolute vaccine efficacy VE relative to placebo was assessed in young healthy adults in studies PSC04 and PSC01, and was calculated as $(1 - \text{Relative Risk}) \times 100$. In the pivotal clinical endpoint study, PSC04, was powered to assess the lower bound of the two-sided 95% CI of VE around a point estimate of 70%. The acceptance criterion for this endpoint was that the LB of the 95% CI for VE of Flublok relative to placebo should be $\geq 40\%$.
- For the active control (Fluzone) studies in healthy older adults and older adults at greater risk for influenza and its complications (PSC06 and PSC03 respectively), Relative Risk (RR) of influenza illness was calculated with 95% CIs as $(\text{illness rate in Flublok} / \text{illness rate in Control})$. For these studies, a Relative Rate of Efficacy (RE) (or % Relative Reduction) of Flublok to Fluzone was calculated as $(1 - \text{RR}) \times 100$.
- Clinical endpoint data from PSC01 and PSC03 were submitted with the original BLA, while clinical efficacy data from PSC04 and PSC06 were submitted with the CR in April 2009. With submission of the clinical endpoint data in 2009, the Applicant sought traditional approval for Flublok.
- Influenza Illness (ILI) Evaluation for each study was assessed using a Flu Symptom scoring card distributed to each subject. Subjects recorded their symptoms on this card, and if they scored 2 or more points, they were instructed to contact the clinic for an ILI evaluation. The Flu Symptom Score was derived by the sum of the following:
 - 1 point for fever of 100°F or higher;
 - 1 point for any of the following: cough, sore throat, runny nose/stuffy nose;
 - 1 point for any of the following: muscle or joint aches, headache, chills/sweats, tiredness/malaise.

- CDC-ILI was defined as the presence of fever >100°F accompanied by sore throat, coughing or both on the same or on consecutive days.

Reviewer comment: *This definition was slightly modified from the official CDC case definition of ILI (temperature of 100°F [37.8°C] or greater and a cough and/or a sore throat in the absence of a known cause other than influenza), but for the purposes of this review, will be called “CDC-ILI” as it was in the study protocols.*

8.1.1 Trial #1

8.1.1.1 Applicant’s Protocol Number PSC04 (BB-IND 11951) “Evaluation of the Immunogenicity, Safety, Reactogenicity, Efficacy, Effectiveness and Lot Consistency of Flublok Trivalent Recombinant Baculovirus-Expressed Hemagglutinin Influenza Vaccine in Healthy Adults Age 18 to 49 Years.”

8.1.1.1.1 Objective/Rationale:

Primary Objectives:

- Safety: To determine the safety relative to placebo of a single dose of Flublok containing 135µg of total rHA as determined by the rates of adverse events AEs and the observation of systemic and local reactions.
- Lot consistency: To demonstrate clinical consistency among three different lots of Flublok administered during the study. The primary immunogenicity hypothesis was that, for each strain contained within Flublok, the 2-sided 95% CI for the ratio of post-vaccination GMTs of HAI antibody for Lot A vs. B, Lot A vs. C and Lot B vs. C would fall within 0.67 to 1.5.
- Efficacy: to determine the efficacy, relative to placebo, of a single dose of Flublok containing 135µg of total rHA in the prevention of culture-confirmed CDC-ILI due to strains contained in the vaccine. CDC-ILI was defined as fever of ≥100°F oral accompanied by cough and/or sore throat on the same day or on consecutive days.

Secondary Objectives:

- To establish the immunogenicity of a single dose of Flublok for all three lots combined and for each strain contained in the vaccine as demonstrated by the proportion of subjects with a post-vaccination 4-fold rise in HAI titer to at least 1:40 (SCR) and the proportion of subjects with a post-vaccination titer of at least 1:40.
- To determine the efficacy of Flublok, relative to placebo, in the prevention of culture-confirmed symptomatic influenza (not necessarily CDC-defined ILI) due to strains represented in the vaccine in a population of healthy adults aged 18-49 years.

Exploratory Objectives:

- To determine the efficacy of Flublok relative to placebo in the prevention of CDC-ILI due to culture-confirmed influenza due to any influenza virus strain.

- To determine the efficacy of Flublok relative to placebo in the prevention of CDC-ILI regardless of culture results.

Reviewer's comment: Only selected data pertaining to exploratory objectives will be discussed in this review.

8.1.1.1.2 Design Overview

PSC04 was a Phase 3, prospective, randomized, modified double-blind, placebo-controlled multi-center study to evaluate the safety, immunogenicity, lot consistency and clinical efficacy of Flublok relative to placebo. 4648 healthy adults age 18-49 years were enrolled at 23 sites in the United States prior to the onset of the 2007-2008 influenza season. All subjects were stratified according to receipt of influenza vaccine during the 2006-2007 influenza season, and were then randomized within the two strata 1:1 to receive either a single dose of Flublok 135µg or placebo. After randomization, the Flublok group was further stratified into three lots, A, B, and C. An immunogenicity subset of 391 subjects at 5 sites was also selected for the clinical lot consistency study. Reactogenicity events were collected from Day 0 through Day 7. Unsolicited AEs and SAEs were collected through Day 28 in all subjects, at a clinic visit for subjects in the immunogenicity subset and by telephone contact in the remaining subjects. The immunogenicity subset of subjects had blood drawn on Days 0 and 28 for HAI titers.

Subjects with respiratory illnesses or flu symptoms were identified both by passive reporting by subjects prior to and during influenza season, and also by active weekly telephone follow-up by study personnel during influenza season. Subjects were instructed to contact the clinic for illness evaluation and viral cultures if they recorded an influenza symptom score of 2 or greater on the Flu Symptom Card. Active surveillance was to begin when 8% of national CDC surveillance isolates were positive for influenza. Subjects were asked to participate in the study for at least 6 months, and until the end of the influenza season (EOIS), defined as when the proportion of positive clinical specimens from national CDC surveillance data dropped below 10%. SAEs were followed for at least 180 days and until the EOS visit (approximately 6 months). All AEs and SAEs were followed until resolution or stabilization.

Duration – the Interim Study Period and Complete Study Report

- First subject enrolled: September 15, 2007.
- Last subject completing Day 28 contact: November 20, 2007.
- Interim Analysis Database lock – December 14, 2007.
- Last subject completed at End of Influenza Season/End of study – May 28, 2008.

8.1.1.1.3 Population

The study population was to be composed of 4300 healthy individuals ages 18 to ≤49 years, drawn from the general population of the 23 participating sites, who met all inclusion criteria and who did not meet any exclusion criteria.

Exclusion criteria

Noteworthy exclusion criteria included the following:

- Presence of high-risk conditions or other characteristics considered to be indications for influenza vaccination, as defined by the Advisory Committee on Immunization Practices (ACIP).
- Use of experimental vaccines or any influenza vaccine after May 31, 2007 for the Southern Hemisphere or the 2007-2008 Northern Hemisphere epidemic seasons.

8.1.1.1.4 Products Mandated by the Protocol

A 0.5mL dose of Flublok was administered once on Day 0 IM in the non-dominant deltoid muscle. Each dose contained a total of 135µg of rHA as determined by SRID, representing the three recommended strains of influenza virus for the 2007-2008 Northern Hemisphere influenza season:

- 45µg rHA A/Solomon Islands/03/2006 (H1N1)
- 45µg rHA A/Wisconsin/67/2005 (H3N2)
- 45µg rHA B/Malaysia/2506/2004 (B strain)

Total 135µg HA antigen per 0.5 mL dose.

The three lots of Flublok tested in the study were: Lot 50-07010 (Lot A); 50-07011 (Lot B); and 50-07014 (Lot C).

Placebo: 0.5mL normal saline for injection, USP, administered IM once on Day 0 in the non-dominant deltoid, also stored at 2-8°C until use.

8.1.1.1.5 Endpoints

Primary Safety Endpoints

- Frequencies of solicited local and systemic reactions (reactogenicity events) in the 7 days following vaccination, as noted on the subject memory aid and collected by telephone interview 8-10 days post-vaccination.
- Frequencies of AEs (unsolicited and/or treatment-emergent) that occurred in the 28-day period following vaccination as assessed on the Day 28 visit or phone call.
- Serious adverse events (SAEs) were collected through December 14, 2007 when the database was locked for the interim analysis.

Reviewer comment: For the Interim Study Report submitted to the original BLA, SAEs occurring from Day 0 through Day 28 were reported. SAEs were collected for a total of 6 months and final results were reported in the CSR submitted in the Applicant's Complete Response April 7, 2009.

Primary Immunogenicity Endpoint: Clinical lot consistency

- GMTs for subjects in the immunogenicity subset were calculated for each strain and lot. The 2-sided 95% CI for the ratio of pre-vaccination to post-vaccination GMTs for Lot A vs. B, Lot A vs. C, and Lot B vs C was computed (post-vaccination GMTs were computed with pre-vaccination titres serving as co-variates).
- Lot Consistency Hypothesis (Ha): Clinical Lot Consistency would be demonstrated if, for each strain, the 2-sided 95% CI for the ratio of post-vaccination GMTs for Lot A vs. B, Lot A vs. C, and Lot B vs. C fell entirely

within 0.67 to 1.5. The Applicant calculated that the sample size of 150 subjects per lot was sufficient to establish lot consistency using an overall $\alpha = 0.05$, and individual test power of 97.55% and an overall power of at least 80%.

Secondary Immunogenicity Endpoints and Criteria for Success:

- Seroconversion: defined as the proportion of subjects with either a 1) pre-vaccination HAI titer $< 1:10$ and a post-vaccination titer $\geq 1:40$, or 2) a pre-vaccination HAI titer $\geq 1:10$ and a minimum 4-fold rise in post-vaccination titer. For each strain contained within Flublok, by Day 28 the lower bound of the 2-sided 95% CI of the proportion of subjects achieving seroconversion must meet or exceed 40%.
- Proportion of Subjects Achieving a post-vaccination HAI Titer $\geq 1:40$ ($\% \geq 1:40$). For each strain contained within Flublok, by Day 28 the lower bound of the 2-sided 95% CI of the proportion of subjects with a post-vaccination HAI titer of $\geq 1:40$ must meet or exceed 70%.

Serologies

- The immunogenicity endpoints were assessed by measuring HAI titers to each of the vaccine antigens. The assays were performed by a single laboratory (CCHMC) using BEVS-derived test antigens supplied by PSC and turkey red blood cells. Lower limit of detection (LOD) was 1:10.
- Validation of the HAI assay: Please see Section 4.4 of this review.

Reviewer comment: The statistical reviewer noted unusual variability in GMTs within lots (assay variability), between lots and between studies. The Applicant was asked to explain this variability (Statistical IR August 14, 2009). The Applicant's response contained results that did not demonstrate the same degree of variability. Please see the discussion and resolution of this issue in Sections 4.4 and 9 of this review.

Primary Efficacy Endpoint

- The proportion of subjects in each treatment group who experienced cell-culture confirmed CDC-ILI during the 2007-2008 influenza epidemic season associated with isolation of an influenza virus antigenically resembling the vaccine strain from a nasal/throat swab (NS/TS) specimen collected during the acute illness.
- CDC-ILI was defined as the presence of fever $>100^{\circ}\text{F}$ accompanied by sore throat, coughing or both on the same or on consecutive days.
- Antigenic relatedness was confirmed by reciprocal HAI testing using ferret antisera.
- Vaccine Efficacy (VE) was computed as: $VE = (1 - RR) \times 100 = (1 - P_v/P_p) \times 100$ [where RR = relative risk, P_v =proportion of Flublok recipients who developed cell-culture-confirmed CDC-ILI, and P_p =proportion of Placebo recipients that developed cell culture-confirmed CDC-ILI].
- Primary efficacy hypotheses
 - H_0 (null hypothesis): The lower bound of the two-sided 95% CI of VE of Flublok relative to placebo will be $< 40\%$, where $VE = (1 - P_v/P_p) \times 100$

- Ha (alternative hypothesis): The lower bound of the two-sided 95% CI of VE of Flublok relative to placebo will be $\geq 40\%$, where $VE = (1 - P_v/P_p) \times 100$

Secondary Efficacy Endpoints

- Proportion of subjects in each treatment group who experienced cell-culture-confirmed respiratory illness (not necessarily CDC-ILI) during the 2007-2008 influenza epidemic season associated with isolation of an influenza virus antigenically resembling the vaccine strain from a NS/TS collected during the acute illness. See Section 8.1.1.1.6 for ILI surveillance and definition as a flu symptom score of 2 or greater.

Exploratory Endpoints

- The proportion of subjects in each treatment group who experienced cell-culture-confirmed CDC-ILI during the 2007-2008 influenza epidemic season associated with isolation of any influenza virus strain from a NS/TS collected during the acute illness.
- The proportion of subjects in each treatment group who experienced cell-culture-confirmed CDC-ILI during the 2007-2008 influenza epidemic season regardless of culture results.

Reviewer comment: Comparison of the final study protocol and the final Complete Study Report indicate that the pre-specified safety and immunogenicity endpoints were not modified following analysis of the data.

Adverse events were defined as any event, side effect, or other untoward medical occurrence, including dosing errors that may be present during treatment with a pharmaceutical product and may or may not be related to treatment. AEs were to be monitored after vaccination as follows:

- Reactogenicity (solicited) events: the frequency of local and systemic reactions for 8 days following vaccination (Day 0 through Day 7), noted on the subject Memory Aid and assessed on the Day 8 contact.
- Local (injection site) reactions: pain, bruising, measured redness, measured swelling. Grading scale for injection site redness or swelling:
 - Grade 0= measured $<10\text{mm}$
 - Grade 1= measured $\geq 10\text{mm}$ and $< 20\text{mm}$
 - Grade 2= measured $\geq 20\text{mm}$ and $< 50\text{mm}$
 - Grade 3= measured $\geq 50\text{mm}$.
- Systemic reactions:
 - Fever ($\geq 100^\circ\text{F}$)
 - Fatigue, lack of energy
 - Shivering (chills)
 - Joint pain
 - Muscle pain
 - Headache
 - Nausea
- Grading scale for fever:

- Mild: 100.4°F to ≤101.1°F
 - Moderate: 101.2°F to ≤102.1°F
 - Severe: ≥102.2°F
- Unsolicited Adverse Events: Treatment-emergent AEs that occurred in the 28-day period following vaccination, as assessed on the Day 28 clinic visit or telephone call.
- All AEs were recorded in the Source Document Worksheets (SDWs) and then entered into the electronic CRF.
- The site investigator was to evaluate all AEs as to severity and relationship to the study vaccine, report action taken, and follow until clinically resolved or stable.
- Toxicity Grading Scale for AEs: signs and symptoms were graded by the investigator using the NCI Common Toxicity Criteria (CTCV3) and graded as mild, moderate, or severe according to the following definitions:
 - Mild: caused no limitation of usual activity
 - Moderate: caused some limitations of usual activities
 - Severe: caused inability to carry out usual activities.
- SAEs were defined in accordance with 21 CFR 312.32.
- AEs were assessed as not related, possibly related or related to the study treatment by the investigator.
- All AEs and SAEs were classified by body system and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number of subjects and percentages were summarized by: body system and PT; body system, PT and severity; and body system, PT, and relationship to study medication.

8.1.1.1.6 Surveillance/Monitoring

All subjects were observed for at least 15 minutes immediately following vaccination and were contacted by telephone on Day 8 by study personnel to solicit reactogenicity symptoms for Day 0 to Day 7 of the Memory Aid. AE and concomitant medication information from these contacts were recorded by study personnel on SDWs.

On Day 0 and Day 28, subjects in the immunogenicity subset had blood drawn for HAI serologies, a medical history review and a targeted physical exam if indicated. Changes in health status, concomitant medications, and AEs were reviewed and recorded. Subjects who were not in the immunogenicity subset did not return for a clinic visit, but were contacted by study personnel to evaluate any change in health status, concomitant medications and AEs.

Follow/up Phone Calls/Flu Surveillance

- Active surveillance for influenza was to begin when national CDC surveillance data showed that 8% of specimens tested were positive for influenza, unless local data showed that influenza was circulating in the study site region, in which case the site would begin surveillance based on local data. Surveillance was to end when fewer than 10% of specimens tested by national CDC surveillance were positive for influenza. This time point was defined at the End of Influenza Season (EOIS).

- During this flu-surveillance period, subjects were to receive weekly phone calls from study personnel to elicit information regarding the presence or absence of respiratory illness symptoms. If subjects had recorded an influenza symptom score of 2 or greater on the Flu Symptoms Card, they were instructed to contact the clinic to arrange an illness evaluation.
- During these surveillance calls, changes in health status and SAEs were also solicited.

Illness Evaluations

- Subjects were instructed to record respiratory symptoms on weekly Flu Symptoms Cards beginning on Day 0. Subjects with flu symptoms score of 2 or greater were to contact study personnel and return to clinic within 24-72 hours. For those too sick to travel, a study site nurse could make a home visit.
- At the clinic visit, subjects had an interval medical history and physical exam. NS/TS were to be obtained for viral culture. The Flu Symptoms Card was to be collected and replaced with a new card to document the remainder of the illness.

End of Study Evaluation/EOIS

- At the EOIS a final phone call was to be made to record SAEs, any other change in health status, concomitant medications, and to review the Flu Symptoms Card.
- SAEs were to be followed until resolution or stabilization.

Reviewer comment: Sample Reactogenicity Memory Aid, Flu Symptoms Card, Case Report Form including Day 8 and Day 28 Telephone Assessment Cards, Telephone Scripts for active weekly flu surveillance, End of Study Record Card were reviewed and appeared appropriate.

AE Recording and Follow-up

- All AEs were recorded in the SDWs and then entered into the electronic CRF.
- The site investigator was to evaluate all AEs as to severity and relationship to the study vaccine, report action taken, and follow until clinically resolved or stable.

SAE Reporting

- Life-threatening SAEs or death except those considered unrelated to the study vaccine were to be reported via telephone to the Applicant or Medical Monitor within one business day of site awareness of the event. All other SAEs were to be reported within 3 business days of site awareness of the event by completing the SAE form.
- All SAEs were to be reported on the SAE form and recorded in the SDWs. A VAERS-type report form was to be completed within 48 hours of the initial report.

Pregnancies

- All pregnancies occurring during the study were to be reported as an AE.
- Each pregnancy was to be followed to term, and the Investigator was to record a narrative describing its course and outcome.
- Independent Data Monitoring Committee (DMC)
- To ensure compliance with Applicant, CGP, International Conference on Harmonization (ICH), and regulatory guidelines, data was monitored and audited by –b(4)–, a CRO. The Applicant states that all data was 100% source verified.

- -b(4)- collected and reviewed the quality of the interim safety and HAI data through the Day 28 visit database lock.
- A second independent CRO (-b(4)--) performed the interim statistical analysis based on the interim dataset furnished by -b(4)--.

8.1.1.1.7 Statistical Considerations

- Please see the statistical review by Dr. Barbara Krasnicka.
- Randomization: Subjects who met eligibility criteria were enrolled and stratified based on whether they received influenza vaccine during the 2006-2007 influenza season. They were then randomized using block randomization into three lots: A, B, or C for the Flublok group, or into the placebo group. A 1:1 ratio was to be maintained for the Flublok:placebo treatment groups, and a 1:1:1 ratio was to be maintained for the three lots.
- Blinding: The study was double-blinded. Investigator, Applicant and subjects were blinded to treatment assignment. To reduce variability and bias, a centralized laboratory blinded to lot, subject and study site performed the HAI assays.
- Subjects who were lost to follow-up or who terminated early were not replaced.
- Subject Demographics: summary statistics were calculated for race/ethnicity, gender and age for each treatment group and overall.
- Endpoints: please see section 8.1.1.1.5.
- Analysis Populations
 - Safety Population: all randomized subjects who received Study Vaccine according to the treatment actually received (Flublok or placebo). The Safety Population was used for all safety analyses.
 - Evaluable Population for Immunogenicity (Per Protocol): all subjects who met the study entry criteria, had no major protocol violations, and had titers taken at baseline (Day 0) and after vaccination (Day 28), categorized according to treatment actually received.
 - Evaluable Population for Clinical Efficacy – all subjects who met eligibility criteria, were randomized, had no major protocol violations, and completed at least 50% of follow-up telephone contacts, including the EOIS call, categorized based on actual treatment received.

Reviewer comment: The Applicant used the Safety Population as the denominator for the Clinical Efficacy Analyses rather than the Evaluable Population for Efficacy as defined in the Statistical Analysis Plan (SAP). The statistical reviewer was not able to determine an appropriate denominator based on the information submitted in the datasets, and was therefore not able to perform sensitivity analyses. However, the larger Safety Population denominator used in the Applicant's analyses would be expected to result in a more conservative or lower estimate of VE than if the smaller Evaluable Population denominator had been used. Approximately equal proportions of subjects in the Flublok vs Placebo groups completed the study (87% vs 88%). Use of the Safety Population for the Clinical Efficacy Analyses did not change the overall results or conclusions.

- Immunogenicity analysis
 - Serum HAI antibody response data were summarized. Frequency count and percentage of subjects with no increase, 2-fold, and ≥ 4 -fold increase of baseline serum HAI antibody were presented for Day 28 (vs Day 0) for the Flublok group only (combined, and for the Lot A, B and C subgroups). Blood specimens obtained from the placebo recipients were not tested by the central laboratory.
 - Frequency count and percentages of subjects with or without a 4-fold or greater increase were presented for the Flublok group only (combined, and for Lot A, B and C subgroups).
 - HAI antibody GMTs for the Flublok group overall and lot-specific subgroups at Day 0 and Day 28 were evaluated by a repeated measure ANOVA. A 2-sided 95% CI around the GMT was calculated.
- Determination of Sample Size for the Lot Consistency Sub-study
 - To compare the GMT ratios of all three lots of Flublok for each strain contained in the vaccine, and to demonstrate the primary endpoint that the 2-sided 95% CI for each of these GMT ratios should fall within 0.67 and 1.5, a sample size of 150 subjects for each lot was selected. The Applicant calculated that this sample size was sufficient for nine individual comparisons (three lot-to-lot pair-wise comparisons for each of three strains) with an individual test power of 97.55% and an overall power of at least 80% with an $\alpha=0.5$.
- Determination of Sample Size for Efficacy
 - The sample size was selected based on the assumptions that Flublok would be at least 70% efficacious relative to placebo as measured by VE, that the placebo attack rate would be at least 3%, and that the attrition rate would be 5%. The efficacy hypothesis (H_a) was that, for a sample size of 4318, the study should demonstrate with 80% power that the LB of the 95% CI for VE against matched strains was greater than 40%.
- Descriptive statistics were used to summarize safety endpoints.
 - Reactogenicity events were summarized by type, frequency count and percentage, and severity for each treatment group and overall along with 95% CIs.
 - Unsolicited AEs were summarized by MedDRA system organ class (SOC), PT, number of subjects and percentages, severity, and relationship to study medication for each treatment group and overall.
 - The Applicant provided an estimate of the probability of detecting a rare adverse event based on the Poisson distribution and given the sample size used in this study (submitted in a response to IR, STN 125285/0.4, June 16, 2008). Using this analysis, the Applicant indicated that the likelihood of detecting an AE with a rate of 1 per 1000 for this study was 90.4% and for an AE with a rate of 3 per 1000, 99.9%.

Reviewer comment: During pre-BLA discussions, the proposed sample size and potential to detect relatively rare AEs was considered appropriate in view of the new manufacturing process used to make the investigational product.

- Changes in the Conduct of the Study or Planned Analyses
 - Site 13, Los Angeles, CA, immunogenicity sub-study site: According to the Applicant, the randomization code had not been received from the CRO when the first group of subjects, n=37, was waiting to be vaccinated. Because neither the Applicant nor the CRO could be reached, the Investigator made a decision to randomize these initial subjects into four equal groups (Lot A, Lot B, Lot C and placebo) rather than first into two groups Flublok and placebo followed by sub-randomization of the Flublok group into three Lot subgroups. The Applicant states that, because subjects were randomly allocated to the treatment arms, this change in the randomization procedure for Site 13 should not introduce bias into the comparison of lots and treatment groups within this site. It may result in a lower power for the clinical efficacy analysis because of the relatively fewer subjects in the placebo group. The Applicant performed an analysis of results for Site 13 compared to the other four immunogenicity sub-study sites.

Reviewer comment: The Applicant's explanation for the change in the randomization procedure and conclusions regarding potential introduction of bias into the analysis appears to be reasonable. For further discussion of this issue, please see the statistical review.

- Immunogenicity subset: 450 subjects, 150 per lot, were planned for this subset. In the original BLA submission, April 18, 2008, the Applicant presented immunogenicity data for 391 subjects in the ISR. However, the statistical reviewer found that 480 subjects were actually vaccinated and that 393 subjects had HAI titers in the electronic dataset for the immunogenicity analyses. Please see the Results Section 8.1.1.2.1 Disposition of Subjects below for further discussion of this discrepancy and the Applicant's Complete Response.
- Failed lot-to-lot consistency comparison for the H3 antigen. Failure of the lot-to-lot consistency comparison for H3 antigen prompted the Applicant to calculate and compare SCRs, proportion of subjects with post-vaccination HAI titers of $\geq 1:40$, and AEs for each of the three lots. Additional analyses were performed to evaluate clinical efficacy by lot to assess the potential impact of failed lot consistency on clinical efficacy.

Reviewer comment: These results will be reviewed in the results section.

8.1.1.2 Results Study PSC04

8.1.1.2.1 Populations Enrolled and Analyzed

Subject Disposition – Complete Study Report

Reviewer comment: The original submission, April 2008, required a CR to FDA questions regarding randomization errors and missing serologic data. The Applicant's CR (April 7, 2009, items 13a and b) satisfactorily accounted for the disposition of all subjects.

- A total of 4648 subjects were enrolled, randomized, and vaccinated. Due to a randomization error at Site 13 (see Section 8.1.1.1.7 above, Changes in Conduct of the Study), the actual number of subjects vaccinated in each group was: Flublok n=2344 and Placebo n=2304

Reviewer comment: BIMO was asked to investigate Site 13 because of the randomization error that occurred there, and concluded that there were no significant deficiencies that would preclude approval of Flublok.

- 4071 subjects (88%) completed the study procedures through Day 180.
- There was one death and three discontinuations due to AEs in each treatment group. All occurred after Day 28 and none were considered related to Flublok.
- There were a total of 577 (12%) discontinuations by the end of the study, Flublok n=295 and placebo n=282. Of the Flublok discontinuations, 260 (88%) of all discontinuations) were lost to follow-up and 22 (7%) withdrew consent. Of the placebo discontinuations, 251 (89%) were lost to follow-up, 14 (5%) withdrew consent. Reasons for withdrawal among the Flublok group were evaluated by means or the datasets, and included "relocation, lost interest, too busy, lost to follow-up and pregnancy".
- Thirty-two subjects in the immunogenicity subset (6.7%) did not have HAI results available for the final study report: 28 were lost to follow-up; 2 withdrew consent prior to Day 28 serology; and 2 subjects' samples were lost by the site (Site 13).
- Table 3 presents the disposition of subjects through Day 180 and is based on the Applicant's CR Table 4 Module 5 Volume 2 Section 10.1, p 56, and Table 14.1.1, p 158. The tabular data were confirmed by evaluation of the electronic datasets.

Table 3 CSR – Final Disposition of Subjects through Day 180 – PSC04

Disposition	Placebo N (%)	Flublok N (%)	Overall N (%)	Flublok Immunogenicity Subset N(%)
Randomized	2325 (100)	2323 (100)	4648 (100)	480 (100)
Vaccinated	2304 (100)	2344 (100)	4648 (100)	480 (100)
Completed	2022 (88)	2049 (87)	4071 (88)	402 (84)
Discontinued	282 (12)	295 (13)	577 (12)	78 (16)
-Due to AE	3 (<1)	3 (<1)	6 (<1)	0
-Lost to follow-up (by Day 28)	85 (4)	88 (4)	173 (4)	0
-Lost to follow-up (by end of study)	251 (11)	260 (11)	511 (11)	73 (15)
-Withdrew consent	14 (1)	22 (1)	36 (1)	5 (1)
-Death	1 (<1)	1 (<1)	2 (<1)	0
-Randomized, not vaccinated	0	0	0	0
-Other reasons	13 (1)	9 (<1)	22 (<1)	0
Safety Population	2304	2344	4648	
Evaluable Population for immunogenicity*	n/a	n/a	n/a	448

*Serology available for immunogenicity analysis post database lock

Reviewer comment: *VRBPAC members commented that a lost to follow-up rate of 11% at Day 180 in study PSC04 was an important omission or loss of safety data, especially for rare events. The majority of the discontinuations came from 7 of the 24 study sites, each of which had a lost to follow-up rate of >5% by the end of the study. The discontinuation and lost to follow-up rates for PSC04 through Day 28, however, were 4%, and for the other clinical trials these rates were ≤ 2%. One would expect that most common vaccine-related reactions including hypersensitivity reactions would have occurred and would have been captured within the 28 days post-vaccination. Accordingly, it is this reviewer’s perspective that, while the loss to follow-up reported in this study is a limitation, it does not significantly compromise the safety data obtained from this investigation.*

Protocol Deviations

A total of 80 versus 62 protocol deviations were identified in the Flublok and placebo groups, respectively. Thirty-seven of the Flublok group deviations resulted from improper randomization at Site 13.

Reviewer comment: *An amended Protocol Deviations report in the CR included the 37 randomization errors at Site 13 originally omitted from the report. Aside from these randomization errors, there do not appear to be other significant imbalances between the treatment groups. The Applicant believes that the alternate scheme used to randomize the 37 subjects at Site 13 should not have introduced bias. The Applicant presents a post-hoc exploratory analysis of immunogenicity by site that demonstrates*

similar results for Site 13 as compared to the other 4 immunogenicity sites. For further discussion of this issue, please see the statistical review.

Sixteen subjects in the immunogenicity subgroup returned for the Day 28 contact and serologies outside the pre-specified window (Day 24-Day 36). Because serologies were drawn between Day 21 and Day 51, the Applicant did not exclude them from the immunogenicity analyses.

Reviewer comment: *It appears reasonable not to exclude these subjects because the deviations were approximately equal between treatment groups and because serologies drawn 21 to 51 days after vaccination would not be expected to be significantly different from those drawn between Days 24 and 36.*

Demographic Data

Demographic characteristics of the safety and evaluable populations for study PSC04 are presented in Table 4:

Table 4 Demographics Safety and Evaluable Populations – PSC04

Category	Characteristic	Flublok Safety Population N=2344 (%)	Flublok Evaluable Population (Immunogenicity Subset) n=391 (%)	Placebo Safety Population N=2304 (%)
Race/Ethnicity	White/ Caucasian	1570 (67)	256 (65)	1530 (66)
Race/Ethnicity	Black/ African-American	430 (18)	73 (19)	447 (19)
Race/Ethnicity	Latino/Hispanic	250 (11)	36 (9)	239 (10)
Race/Ethnicity	Asian	62 (3)	21 (5)	52 (2)
Race/Ethnicity	American Indian/ Alaska Native	7 (<1)	1 (<1)	9 (<1)
Race/Ethnicity	Native Hawaiian/ Pacific Islander	6 (<1)	1 (<1)	8 (<1)
Race/Ethnicity	Other	19 (1)	3 (1)	19 (1)
Gender	Male	953 (41)	176 (45)	955 (41)
Gender	Female	1391 (59)	215 (55)	1349 (59)
Age (years)	Mean (SD)	32.5 (9.3)	32.9 (9.98)	32.5 (9.17)
Age (years)	Median	32.0	31.0	32.0
Age (years)	Minimum/Max	18, 55	18, 49	18, 50

Source: Applicant's Tables 14.1.3 and 14.1.4 Module 5 Volume 19 Section 5.3.5.1.3, p 130-131; confirmed by evaluation of the electronic datasets

The majority of subjects were Caucasian, 67% for Flublok, 66% for placebo, and female, 59% for both groups.

The mean age was 32.5 years, with a range of 18 to 55 years. Three protocol deviations included subjects who provided an incorrect birthdate at study entry. These subjects were not withdrawn and explain why the maximum age in both treatment groups is greater than the per protocol age maximum of 49 years.

Reviewer comment: *There were no significant demographic differences among the study groups. The protocol deviations that involved incorrect date of birth for three subjects should not significantly impact the study endpoints. These subjects were included in the safety and immunogenicity analyses.*

Actual date of Day 28 Serology

The majority of subjects (99%) had serologies drawn within a window of Day 24 to 35 (the pre-specified window was Day 24-36).

Influenza History

Of Flublok recipients in the immunogenicity subset, 83 had received TIV and 308 had not received TIV in the previous influenza season.

8.1.1.2.2 Efficacy endpoints and outcomes, summary of the Applicant's analyses:

The immunogenicity analyses were performed on the Evaluable Population (n=391), those subjects in the Flublok immunogenicity subset who had serologies drawn on Day 0 and Day 28.

Primary Immunogenicity Endpoint: Lot-to-Lot Consistency

- For each strain contained within Flublok, GMTs for subjects in the immunogenicity subset were calculated for each strain and lot. The 2-sided 95% CI for the ratio of pre-vaccination to post-vaccination GMTs for Lot A vs. B, Lot A vs. C, and Lot B vs C was computed (i.e., post-vaccination GMTs were computed with pre-vaccination titres serving as co-variates).
- Clinical lot consistency was demonstrated if, for each strain, the 2-sided 95% CI for the ratio of post-vaccination GMTs for Lot A vs. B, Lot A vs. C, and Lot B vs. C fell entirely within 0.67 to 1.5.
- Three batches were used to formulate each Flublok Drug Product Lot (Table 5).

Table 5 Flublok Drug Substance Batches Used to Formulate Clinical Drug Product Lots – PSC04

Strain	A/Solomon Islands/ 03/2006 (H1)	A/Wisconsin/ 67/2005 (H3)	B/Malaysia/ 2506/2004
Flublok Drug Product Lots	Flublok Drug Substance Batch	Flublok Drug Substance Batch	Flublok Drug Substance Batch
50-07010 (Lot A)	--b(4)----	--b(4)----	--b(4)----
50-07011 (Lot B)	--b(4)----	--b(4)----	--b(4)----
50-07014 (Lot C)	--b(4)----	--b(4)----	--b(4)----

- Each drug product lot was formulated to contain 45µg of each antigen as determined by the single-radial immunodiffusion (SRID) method.
- Lot consistency assessments in the evaluable population, as presented in the Applicant's CR, are presented in Table 6:

Table 6 Lot Consistency – Evaluable Population (n=448) - PSC04 CSR

Strain	Comparison	Ratio	95%CI	Meets CBER Criteria?
H1	Lot A vs. B	1.07	(0.85, 1.36)	YES
	Lot A vs. C	0.91	(0.71, 1.15)	
	Lot B vs. C	0.85	(0.67, 1.07)	
H3	Lot A vs. B	2.03	(1.56, 2.64)	NO
	Lot A vs. C	1.63	(1.26, 2.11)	
	Lot B vs. C	0.80	(0.62, 1.04)	
B	Lot A vs. B	0.88	(0.69, 1.13)	YES*
	Lot A vs. C	0.85	(0.64, 1.09)	
	Lot B vs. C	0.96	(0.73, 1.23)	

*missed one comparison only by a small margin

Source: CR Table 9, Vol 2, Section 11.1, p66.

- The H3 strain failed to meet the lot consistency criteria.
- The B strain missed the lower bound of the 95% CI for one comparison, Lot A vs. Lot C, by only a small margin.
- The Applicant attributed the failure of the H3 strain to meet these criteria to a lower rHA H3 antigen content with associated lower GMTs to H3 for lots B and C relative to Lot A. Despite the failed lot consistency, an exploratory analysis (see CR below) revealed that the immunogenicity endpoints of seroconversion and the proportion with post-vaccination HAI titer of at least 1:40 were met for all three strains and all three lots. Additionally, a post hoc clinical efficacy analysis by lot for all H3N2 isolates (see CR below) demonstrated similar efficacy for all three lots.

Applicant's Complete Response, April 7, 2009 – Item 15: Lot Consistency

- FDA noted the failure of rHA H3, A/Wisconsin (H3N2), to meet the lot consistency endpoints with 95% CI ranging from 0.56 to 2.64 for the three lots. FDA suggested that pooling of immune response data might not be appropriate in the absence of lot consistency, and requested additional information about the potential cause(s) of the differences between lot A and the other lots.
- The Applicant investigated the batch records for the drug product lots in an attempt to determine the cause of this failure. The Applicant's investigation revealed that, approximately half as much A/Wisconsin protein was included in the drug product formulation for Lots B and C than for Lot A. In the CR, the Applicant calculates that the A/Wisconsin Lot A HA antigen content was 61µg rHA compared to 29µg and 33µg for Lots B and C, respectively. This difference in antigen content translated into higher GMTs for Lot A than for Lots B or C.
- Because of the failed lot consistency for A/Wisconsin and the relatively lower rHA protein calculated for Lots B and C, the Applicant conducted an exploratory analysis of lot specific rates for seroconversion and for the proportion of subjects with post-vaccination titers of $\geq 1:40$. The results demonstrate that these immune response criteria were met by each lot for all three strains. The Applicant also provided an analysis of clinical efficacy against all culture-confirmed H3N2 strains that demonstrated similar results among the three lots. [Data not shown.]

For tabular results, please see CR, April 7, 2009, tables 15-1, 15-2 and 15-3, vol.1, pp9-10.]

Reviewer comment: *The results of the Applicant's assessment of the lot consistency findings suggest that despite the relatively lower rHA content for Lots B and C, i.e., less than 45µg rHA H3 antigen, compared to Lot A, all three lots met the secondary endpoints of FDA immune response criteria for all three strains. Regarding the clinical efficacy analysis, the results among the three lots are very similar. Based on the overall data, it appears acceptable to pool the lot results. The Applicant's data also indicate that the antigen content for the H1N1 and B strains, where lot consistency was demonstrated, ranged from 51 to 64µg across Lots A, B and C. Similar to the H3N2 Lot A, the antigen content for these strains was higher than the target level of 45µg. This is due to -----(b)(4)-----to compensate for loss of potency over time. DVP has noted that the clinical lots for PSC04 were manufactured prior to establishing a validated process. After this trial was conducted, FDA worked with PSC to refine -----(b)(4)----- specifications to ensure consistent HA antigen content in the final trivalent vaccine going forward.*

For additional discussions of these analyses and of the related manufacturing and potency issues, please see the statistical review by Dr. Krasnicka and the CMC Reviews by Drs. Maryna Eichelberger, Matthew Sandbulte, Arifa Khan and Rajesh Gupta.

Geometric Mean Antibody Titers (GMT)

Each vaccine strain demonstrated robust rises in GMT from baseline Day 0 to post-vaccination Day 28 (Table 7):

Table 7 Pre- and Post-vaccination GMTs – ISR (n=391) – PSC04

Strain	H1N1	H1N1	B	B	H3N2	H3N2
Parameter	GMT	95% CI	GMT	95% CI	GMT	95% CI
Day 0	31.26	27.22,35.90	49.75	43.98,56.27	22.36	19.99,25.02
Day 28	360.36	325.04,399.51	192.05	172.01,214.44	257.76	229.04,290.09

Source: CR, Vol 1, p77.

Applicant's Complete Response – April 7, 2009 – Item 16: Variability in GMTs for H3N2

- The Applicant was asked to provide an explanation for the variability in Day 28 GMTs for the H3N2 strain in study PSC04 (396.88, 178.8, and 241.2 for lots A, B, and C respectively) and in studies PSC03 and PSC06 (H3N2 GMTs of 338.35 and 105.1 respectively).
- The Applicant's explanation for the GMT variability in study PSC04 was again that only half as much A/H3N2 rHA protein was used in the formulation for Lots B and C as compared to Lot A. The Applicant noted that despite this, the CBER May 2007 Guidance immune response criteria were met for all three lots, and that the GMTs for Lots B and C were similar with overlapping 95% CIs.
- Regarding studies PSC03 and PSC06, the variability did not appear to be specific to Flublok, but was also observed for Fluzone. The Applicant stated that the explanation for this difference in GMT response between studies/seasons may be

multifactorial. For example, differences in host age and immunocompetence and differences in pre-existing exposure to natural or vaccine strain A/Wisconsin/67/05-like viruses might have contributed to the different immune responses between the two seasons.

Reviewer comment: *While it appears reasonable to accept that the factors noted by the Applicant might contribute to variability in GMTs, the statistical reviewer noted unusual variability in GMTs that appeared to be independent of such variables. The explanation for this variability was not clear to the statistical reviewer, however, variability due to the HAI assay was one possibility.*

Secondary Immunogenicity Endpoints:

Reviewer Comment: *The Applicant's original statistical analysis plan did not include a placebo group for the secondary immune response endpoints. In the August 2008 CR letter, FDA suggested that the integrity of the secondary immune response endpoint results for PSC04 would be strengthened by comparison to a placebo group. This was particularly true for the B strain which had failed to meet immunogenicity endpoints in PSC03 and PSC06. The Applicant agreed to conduct the pre-specified secondary immunogenicity analyses on stored sera from a subset of 127 randomly selected subjects who received placebo in study PSC04 (April 7, 2009 CR, item 14). Results of the pre-specified analyses conducted on the Flublok recipients and the post-hoc analyses conducted on placebo recipients are presented in Table 8:*

Table 8 Secondary Immunogenicity Endpoints: Proportion with 4-fold increase in HAI titer and post-vaccination HAI titer \geq 1:40 – Evaluable Population – Flublok vs Placebo – PSC04

Endpoint	SCR	SCR	% HAI \geq 1:40	% HAI \geq 1:40
Treatment	Placebo n=127	Flublok n=448	Placebo N=127	Flublok n=448
H1				
%	3	78	36	99
95% CI (%)	(0.9,7.9)	73.5,82.2	(27.9,45.2)	(97.1, 99.5)
Pass	NO	YES	NO	YES
H3				
%	3	81	20	97
95% CI (%)	(0.9,7.9)	(77.1,84.6)	(13.8,38.5)	(94.8,98.3)
Pass	NO	YES	NO	YES
B				
%	0	52	37	96
95% CI (%)	(0,2.9)	(47.0,56.5)	(28.6,46.0)	(94.0,97.8)
Pass	NO	YES	NO	YES

Source: CR, Tables 14-1 and 14-2, vol. 1, p6-7.

SCR = % with 4-fold increase in HAI titer to \geq 1:40

% HAI \geq 1:40 = % with post-vaccination HAI titer \geq 1:40

- For the complete immunogenicity population of n=448, 28 days following vaccination, the lower bounds of the 2 sided 95% CIs for the proportion with a four-fold increase in HAI antibody titer to a minimum titer of 1:40 were: 73.5% for H1, 77.1% for H3, and 47.0% for the B strain.

- The lower bounds of the 2-sided 95% CIs for the proportion of subjects whose post-vaccination HAI titer was $\geq 1:40$ were: 97.1% for H1, 94.8% for H3, and 94.0% for the B strain.

Reviewer Comment: The lower bounds of the 2-sided 95% confidence intervals exceeded the pre-specified criteria in the Statistical Analysis Plan for both secondary immunogenicity endpoints for all three strains.

- The Applicant also presented results of GMTs from the placebo group as compared to the Flublok group (data not shown) that showed no change in titer pre- and post-vaccination in the placebo group in contrast to the Flublok group. These results suggest that the investigational agent (Flublok) was responsible for the immune responses observed in the subjects who received Flublok.

Clinical Efficacy Endpoints PSC04

The primary efficacy endpoint for Study PSC04 was the efficacy of a single dose of Flublok relative to placebo in the prevention of cell culture-confirmed CDC-ILI due to strains represented in the vaccine. The secondary efficacy endpoint was the efficacy of a single dose of Flublok relative to placebo in the prevention of cell culture-confirmed ILI, regardless of meeting the CDC case definition, due to strains contained in the vaccine.

Six hundred and forty-six swabs from 582 subjects were obtained from subjects who reported a flu symptom score of 2 or more during the 180-day surveillance period. A total of 64 (2.7%) Flublok and 114 (4.9%) placebo recipients had positive cultures for influenza (Table 9). Of these, 44 (1.9%) Flublok and 78 (3.4%) placebo recipients had culture-confirmed CDC-ILI.

Table 9 Clinical Efficacy – Primary and Secondary Endpoints – Matched strains - PSC04

Virus isolation results	Flublok 135µg N=2344	Placebo N=2304
-Subjects from whom (NS/TS) were obtained, n(%)	273 (11.6)	309 (13.4)
-Subjects with positive cultures, n(%)	64 (2.7)	114 (4.9)
Number of isolates represented in the vaccine	Flublok 135µg N=2344	Placebo N=2304
-B/Malaysia/2506/2004-like	0	0
-A/Solomon Islands/03/2006-like (H1N1)	0	0
-A/Wisconsin/67/2005-like (H3N2)	2	6
Primary Endpoint	Flublok 135µg N=2344	Placebo N=2304
Subjects with culture-positive CDC-ILI, n(%)	1 (0.04)	4 (0.2)
-Vaccine Efficacy, %(95%CI)	75.4 (-148,99.5)	n/a
Secondary Endpoint	Flublok 135µg N=2344	Placebo N=2304
Subjects with culture-positive ILI, regardless of CDC-ILI, n(%)	2 (0.1)	6 (0.3)
-Vaccine Efficacy, %(95%CI)	67.2 (-83.2,96.8)	n/a

Source: CSR Table 23, Vol 2, p81.

NS/TS = nasal swab/throat swab

n/a = not applicable

Reviewer comment: *The 2007-2008 vaccine strains were poorly matched to circulating viral strains. Only 8 of 178 virus isolates (all influenza type A) were antigenically similar to the viral strains included in the vaccine. Fifty-eight of 59 B isolates belonged to the B/Yamagata/16/88 lineage, whereas the B/Victoria-like (B/Malaysia) virus was included in the vaccine.*

- Only 1 Flublok and 4 placebo recipients met primary efficacy endpoint criteria resulting in a point estimate of efficacy of 75.4% (95%CI -148.0, 99.5).
- Only 2 Flublok recipients and 6 placebo recipients met secondary efficacy endpoint criteria resulting in a point estimate of efficacy of 67.2% (95% CI -83.2, 96.8).

Reviewer comment: *Because of the mismatch between the circulating influenza virus strains and the vaccine strains, there were not enough cases to draw reliable conclusions regarding vaccine efficacy for the primary and secondary endpoints.*

Pre-specified Exploratory Endpoint (Table 10)

- The efficacy of a single dose of Flublok relative to placebo in the prevention of culture-positive CDC-ILI due to any strain of influenza regardless of whether the strain was contained in the vaccine. Forty-four (1.9%) Flublok recipients compared to 78 (3.4%) placebo recipients met these criteria for a protective VE of 44.6 % (95%CI 18.8, 62.6).

Table 10 Clinical Efficacy – Pre-specified Exploratory Endpoint – All isolates - PSC04

Virus isolation results	Flublok 135µg N=2344	Placebo N=2304
-Subjects from whom NS/TS was obtained, n(%)	273 (11.6)	309 (13.4)
-Subjects with positive cultures, n(%)	64 (2.7)	114 (4.9)
Number of isolates	Flublok 135µg N=2344	Placebo N=2304
-B/Florida/04/2006-like	23	35
-B/not determined	0	1
-A/Brisbane/59/2007-like (H1N1)	3	9
-A/Wisconsin/67/2005-like (H3N2)*	2	6
-A/Brisbane/10/2007-like (H3N2)	14	27
-A/not determined (H3N2)	17	25
-A/not determined (unknown subtype)	5	12
Exploratory Endpoint	Flublok 135µg N=2344	Placebo N=2304
Subjects with culture-positive CDC-ILI, n(%)	44 (1.9)	78 (3.4)
-Vaccine Efficacy (VE), %(95%CI)	44.6 (18.8,62.6)	n/a

Source: Table 24 CR Vol 2, p 83.

*vaccine match

Reviewer comment: *The pre-specified exploratory endpoint was not restricted to matching strains so that the sample size was greater and the CIs not as wide as for the analyses restricted to matched strains.*

Post-hoc Exploratory Analyses (Table 11)

- The Applicant evaluated all subjects with positive influenza cultures and calculated the protective efficacy against influenza type A and type B.
- For influenza types A and B, VE of Flublok against all culture positive ILIs was 44.8% (LB=24.4%).
- For influenza A, VE of Flublok for those with CDC-ILI was 54.4% (LB=26.1%), and for all positive type A cultures regardless of symptoms/illness, VE was 49.0% (LB=24.7).
- For influenza B, VE of Flublok for those with CDC-ILI was 23.1% (LB= - 49.0%), and for all positive type B cultures regardless of symptoms/illness, VE was 37.2% (LB= - 8.9%).

Table 11 Clinical Efficacy – Post Hoc Exploratory Endpoints – PSC04

Exploratory Endpoint	Flublok 135µg N=2344	Placebo N=2304	VE % (95%CI)
Types A and B –Subjects with culture positive ILI, n(%)*	64 (2.7)	114 (4.9)	44.8 (24.4,60.0)
Type A –Subjects with culture positive CDC-ILI, n(%)	26 (1.1)	56 (2.4)	54.4 (26.1,72.5)
Type A –Subjects with culture positive ILI, n(%)*	41 (1.7)	79 (3.4)	49.0 (24.7,65.9)
Type B –Subjects with culture positive CDC-ILI, n(%)	18 (0.8)	23 (1.0)	23.1 (-49.0,60.9)
Type B –Subjects with culture positive ILI, n(%)*	23 (1.0)	36 (1.6)	37.2 (-8.9,64.5)

Source: Table 25 CR Vol.2, p.85.

VE=vaccine efficacy, Type A=type A influenza, Type B=type B influenza

*ILI = all culture-confirmed cases regardless of whether they met the CDC definition

Reviewer comment: VE results for Flublok against CDC-ILI due to antigenically matched strains are limited by the small numbers of cases. Point estimates of efficacy against both CDC-ILI and culture-positive ILI for all strains regardless of antigenic match were greater than 40%, although the lower bounds of the 95% CI for A strains were 24-26%, and for B strains included zero. For further discussion of the vaccine efficacy results for Flublok across studies, please see the Overview of Efficacy across Trials, Section 9.

Immunogenicity and Efficacy Conclusions PSC04

- In the Applicant's analyses, vaccination of healthy adults 18 to 49 years of age with a single dose of trivalent rHA vaccine 135µg elicited an immune response for which the lower bounds of the two-sided 95% CI exceeded the pre-specified criteria that: 1) proportion of subjects with a four-fold increase in HAI titer to a minimum of 1:40 should exceed 40% and 2) proportion of subjects with a post-vaccination HAI titer \geq 1:40 should exceed 70% for all three antigens strains contained in the vaccine.
- A limitation of the original study design was the lack of a placebo control group for the immunogenicity subset. In the CR, the Applicant conducted the pre-specified immunogenicity analyses on stored sera from a randomly selected subset of the placebo group. The placebo group failed to demonstrate a rise in GMTs and failed to meet the pre-specified immunogenicity endpoints. This suggests that the immune response to vaccination with Flublok was due to the vaccine rather than to potential exposure to circulating influenza virus.

- Lot-to-lot consistency as specified by FDA Guidance was demonstrated for the H1 and B strains. The 2-sided 95% CI of one comparison for B strain, Lot A vs. Lot C, (0.64, 1.12), just missed falling entirely within the guidance criteria of (0.67, 1.5), but the GMT ratio point estimate of 0.85 fell within these margins. The failure of the H3 strain to meet lot consistency criteria was attributed to a lower rHA H3 antigen content with associated lower GMTs to H3 for lots B and C relative to Lot A. Despite the lower rHA H3 antigen content and lower GMTs to H3 for lots B and C, an exploratory analysis revealed that the immunogenicity endpoints of proportion with 4-fold increase and proportion with post-vaccination HAI titer of at least 1:40 were met for all three strains and all three lots.
- According to DVP, the clinical lots for PSC04 were manufactured prior to establishing a validated manufacturing process. After this trial was conducted, FDA worked with PSC to refine –b(4)----- specifications to ensure consistency of the HA antigens in the final trivalent vaccine.
- Flublok failed to meet the primary and secondary efficacy endpoints in the prevention of culture-confirmed influenza against strains included in the vaccine. Likely contributing to this was the antigenic mismatch between vaccine and circulating virus strains. The number of cases caused by antigenically matched strains was too small and CIs were too wide to allow conclusions regarding efficacy against matched strains.
- Vaccine efficacy against the pre-specified exploratory endpoint of prevention of culture-confirmed CDC-ILI due to any influenza strain regardless of antigenic match was 44.6 % (95% CI 18.8, 62.6). Post hoc analyses demonstrated that the point estimate of efficacy for Flublok against culture-confirmed ILI (not necessarily CDC-defined ILI) due to any influenza strain regardless of antigenic match was 44.8%, with a lower bound of 24.4%. Efficacy against any type A strain was 49.0% (LB 24.7%) and to any type B was 37.2% (LB -8.9%). Flublok failed to meet the pre-specified primary efficacy endpoint against matched strains (that the LB of the 95% CI of VE be greater than 40%). However, although FDA does not pre-specify or require that a vaccine demonstrate protective efficacy against strains not included in the vaccine, we do accept that protection against mismatched strains (i.e., cross protection) provides evidence for vaccine efficacy against matched strains. This issue is discussed further in Section 9, Overview of Efficacy across Trials, and Section 12, Conclusions Overall.
- Overall, vaccination with a single dose of 135mcg was immunogenic, and exceeded co-secondary endpoint criteria for immune response. The primary lot consistency endpoint was not met for the H3 strain, but this did not appear to impact clinical safety or efficacy endpoints. The clinical lots were manufactured prior to validation of manufacturing processes, and DVP has noted significant improvements in lot consistency since this study was conducted. Refinements in the –b(4)----- specification have been made to ensure consistent HA antigen content going forward. Limitations associated with concerns over the HAI assay were discussed in Section 4.4 and will be discussed further in Section 9, Overview of Efficacy.
- In an influenza season characterized by a predominance of antigenically mismatched strains, the protective efficacy of Flublok against culture-confirmed

influenza illness due to any virus strain was 44.8% (LB 22.4%). The clinical review team concluded that these data provide evidence of Flublok's efficacy and that it is reasonable to conclude that Flublok would be at least as effective against antigenically similar virus strains in this population.

8.1.1.2.3 Safety Outcomes

The Safety Population was comprised of all 4648 subjects who received a single injection of Study Vaccine including 2344 subjects who received Flublok and 2304 who received placebo. The Applicant used chi-square or Fisher's exact tests to determine significant differences between subjects who received Flublok versus placebo. The statistical reviewer concurred with this analytic approach.

Reviewer comment: The Safety Review was conducted from the source or electronic datasets and will be descriptive in nature. The Applicant's original BLA submission reported AEs through Day 28. The CR updated some AE reporting and reported the occurrence of SAEs, deaths and pregnancies through 6 months post-vaccination.

Deaths and Serious Adverse Events

All SAEs were reviewed by evaluation of the Applicant's summary tables, line listings, Applicant's narratives, and CRFs. Tables 12 and 13 are derived from Applicant's table 14.3.2, Module 5, Volume 19, pp394-395, line listings 16.2.11.1, the Complete Response Vol 2, pp105-149, and the electronic datasets.

Table 12 Serious Adverse Events Occurring in Flublok Recipients through Day 28 – Safety Population – ISR – PSC04

Subject ID	SAE	Severity	Causality*	Treatment	Outcome
02-01049-b(6)	Hepatitis viral	Severe	Not Related	Hospitalization	Ongoing
05-03221-b(6)	Pericardial and pleural effusions	Moderate	Possibly Related	Hospitalization	Resolved without sequelae
13-09740-b(6)	Hand fracture	Moderate	Not Related	Hospitalization and Medication	Ongoing
14-10521-b(6)	Uterine leiomyoma	Moderate	Not Related	Hospitalization	Resolved with sequelae
17-12925-b(6)	Iron deficiency anaemia	Moderate	Not Related	Hospitalization and medication	Resolved without sequelae
20-15524-b(6)	Bipolar disorder and depression	Moderate	Not Related	Hospitalization	Ongoing
23-17853-b(6)	Pyelonephritis acute	Mild	Not Related	Hospitalization	Resolved without sequelae

*causality as assessed by investigator

Source: Table 14.3.2, Module 5, vol 19, pp394-395, line listings 16.2.11.1, CR vol 2, pp105-149, and electronic datasets.

Table 13 SAEs Occurring in Flublok Recipients Day 29 through 6 Months – Safety Population – CSR – PSC04

Subject ID	AE	Severity	Causality	Treatment	Outcome
04-02568-b(6)	Pulmonary Embolism	Severe	Not related	Unknown	Death
04-02458	Liposarcoma	Severe	Not related	Hospital, Meds	Ongoing
01-00426	Appendicitis	Severe	Not related	Hospital	Resolved
02-01450	Cholelithiasis	Mod	Not related	Hospital	Resolved
03-01621	Suicide attempt; Angina; Sinus tachycardia	Severe	Not related	Hospital, Meds	Resolved
04-02528	Tonsillitis	Severe	Not Related	Hospital	Resolved
04-02587	Herniated cervical Disc	Severe	Not Related	Discectomy	Resolved
04-02602	Small bowel Obstruction	Severe	Not related	Hospital	Resolved
04-02622	Suicide attempt	Severe	Not related	Meds	Resolved
04-02658	Worsening uterine Fibroids	Mild	Not Related	Hospital Meds	Resolved
08-05670	Worsening chronic Low back pain	Mild	Not related	Hospital Meds	Resolved
11-08096	Bilat acetabular Fractures	Severe	Not related	Hospital	Resolved
11-08444	Non-cardiac chest pain	Mod	Not related	Hospital	Resolved
14-10558	Left knee torn ACL	Mild	Not related	Hospital	Resolved
15-11327	Abdominal pain; Rt thigh numbness	Mod	Not related	Hospital Meds	Resolved
17-12919	Assault injury	Mod	Not related	Hospital	Resolved
20-15285	Hyperemesis	Mod	Not related	Hospital	Resolved
20-15439	Rt tibial fx; Rt fibula fx	Severe	Not related	Hospital	Resolved
21-16492	Avascular necrosis Lt femoral head	Mod	Not related	Hospital Meds	Resolved
23-17763	Abnormal uterine Bleeding	Severe	Not related	Hospital	Resolved
23-17769	Ovarian cysts; Dysmenorrhea; Menorrhagia; Prolapsed bladder	Severe	Not related	Hospital Meds	Resolved
23-17776	Desynchronous Endometrium	Mod	Not related	Hospital	Resolved

Subject ID	AE	Severity	Causality	Treatment	Outcome
23-17901	Dysfunctional Uterine bleeding	Severe	Not related	Hospital Meds Hysterectomy	Resolved

*causality as assessed by investigator

Source: Table 14.3.2, Module 5, vol 19, pp394-395, line listings 16.2.11.1, CR vol 2, pp105-149, and electronic datasets.

One death occurred in each treatment group through month six (but after Day 28, initial database lock for the ISR); a Flublok recipient who died of a pulmonary embolus and a placebo recipient who died in a motor vehicle accident (a narrative of the death occurring in the Flublok recipient follows). Neither was considered by the investigator or the reviewer as being related to the study vaccine. No deaths occurred in the first 28 days post-vaccination.

- Death from Pulmonary Embolism: Subject 04-02568- b(6), Flublok recipient, was a 47 year old female vaccinated on -----(b)(6)-----, no concomitant vaccines. On -b(6)-----, the subject was hospitalized and died from a pulmonary embolism. The Applicant reports that details were not available because the husband did not have authority to sign for reports. The Investigator assessed this event as not related to the study agent.

Forty-one SAEs in 30 subjects were reported in the Flublok group and 46 SAEs in 35 subjects were reported in the placebo group. Of the Flublok cases, only one, Subject 05-03221- b(6), pleuropericarditis, was considered possibly vaccine-related. None of the cases in the placebo group were considered related to study vaccine. The ISR described SAEs through Day 28 in 7 Flublok recipients and 12 placebo recipients; SAEs through Day 28 involving Flublok recipients are summarized in Table 12. The CSR provides narratives for the additional SAEs reported after Day 28 and through Month 6; SAEs after Day 28 through Month 6 involving Flublok recipients are summarized in Table 13. All narratives were reviewed. The case of pleuropericarditis is presented in detail.

- Pleuropericarditis Case Summary: Subject 05-03221- b(6), Flublok recipient: The SAE report and hospital discharge summary and laboratory reports submitted to IND 11951 Amendment 53 were also reviewed for this subject. At the time of the event, the subject was a 47 year old male from Texas, U.S., who received Flublok on Sept 17, 2007. The subject was diagnosed with both a pericardial and a left pleural effusion on Sept 28, 2007. The SAE required hospitalization on Sept 28, 2007, was judged by the investigator as moderate in severity and possibly related to the study vaccine. Both effusions resolved and the subject was discharged on Oct 10, 2007.

According to the hospital discharge summary, the subject had a history of hypertension for which he took hydrochlorothiazide. He felt well on the day of vaccination Sept 17, 2007. One week prior to admission, he developed fever, cough, shortness of breath, decreased exercise tolerance, and finally chest pain. He self-medicated with ASA, ibuprofen, and Vicks 44D. He presented to his

primary care provider where an echocardiogram revealed a pericardial effusion with cardiac tamponade. He was admitted directly to an intensive care unit in ---- (b)(6)----, where he was found to be afebrile and “somewhat hypoxic”. He underwent prompt cardiac catheterization and drainage of the pericardial effusion on Sept 28, 2007. The fluid was amber, exudative, with an elevated protein content. Culture grew a few *Propionibacterium* species, but multiple subsequent pericardial cultures were negative, and there were not a significant number of white blood cells. The cardiac angiogram revealed a complete occlusion of the left anterior descending artery, but EKG did not reveal acute changes and the subject was not felt to have had an acute myocardial infarction. The subject had a left thorocentesis which was negative. Because of persistent dyspnea and reaccumulation of pleural fluid, bilateral chest tubes and a pericardial window were placed. One pleural fluid sample grew *S. epidermidis*, but multiple other pleural and pericardial fluid cultures were negative and without significant cell counts. Infectious disease consultation felt that the cultures represented contaminants, and did not find a definitive infectious etiology. Viral cultures and titers were negative. Computerized tomography of the chest was otherwise unrevealing as were cardiac enzymes, B-type natriuretic peptide, thyroid stimulating hormone, anti-nuclear antibody, rheumatoid factor, HIV antibody. Liver function tests were mildly elevated, felt to be due to passive congestion, and C-reactive protein was mild-moderately elevated as well, non-specific. The subject improved, chest tube and pericardial drains were removed, and the patient was discharged on Oct 10, 2007 on Toprol XL, furosemide, baby aspirin, and acetomenophen as needed. The discharge diagnosis was possible viral pleuropericarditis.

Accompanying laboratory records confirm that the pleural and pericardial fluid cultures were negative for acid-fast bacilli, fungi, and viral culture including enterovirus and adenovirus. Echovirus, coxsackievirus, cytomegalovirus and Epstein-Barr virus titers were negative. Pleural and pericardial fluid cytology was negative. Peripheral WBC on admission was 18.9, one week later 17.9, and on discharge, 12.1. Hepatitis A and B serologies were negative. The subject received no other vaccines prior to the onset of the SAE.

Reviewer comment: The onset of the pleuropericarditis in this previously healthy 47 year-old male with a history of hypertension occurred within 11 days of vaccination with Flublok. An extensive evaluation failed to determine an etiology. No influenza culture or PCR or enterovirus PCRs were performed on the fluid. Assistance from Pharmacovigilance, OBE, was requested in searching the VAERS database for reports of pleural and/or pericardial effusions associated with influenza vaccines going back to September 15, 2002 through December 31, 2007. The search revealed that pleural and pericardial effusions have been reported rarely to VAERS following influenza vaccination, but these reports are passive and confounded by multiple variables so that one cannot draw firm conclusions regarding the incidence or relatedness to influenza vaccination. The discharge diagnosis for Flublok Subject 05-03221- b(6) was possible viral pleuropericarditis. However, one cannot exclude an idiosyncratic or immune-

mediated hypersensitivity reaction related to the study vaccine. Previous experience suggests that this would be an unusual adverse reaction for a traditional inactivated influenza vaccine. However, Flublok is manufactured in a novel insect cell system. This event will be described in the Adverse Events section (6.1) of the product labeling, and we will request the Applicant to monitor for pleuropericarditis in future trials and as part of the Pharmacovigilance Plan (PVP).

Reviewer comment: Although the onset of this SAE occurred 11 days post-vaccination, it was not until November 16, 2007, approximately 2 months post-vaccination, that the subject was discontinued from the study due to the SAE.

Case narratives for the other six Flublok SAEs that occurred through Day 28 were reviewed. These included cases of viral hepatitis, metacarpal fracture, uterine leiomyoma, iron-deficiency anemia, bipolar disease, and acute pyelonephritis. None were assessed by the investigators as being related to the study vaccine.

Reviewer comment: after review of the case narratives, this reviewer concurs that these other six SAEs most likely were not related to receipt of Flublok.

Reviewer comment: Overall, SAEs and deaths appeared to be balanced between the treatment groups. Only one SAE, pleuropericarditis, appeared possibly related to Flublok, as noted.

Review of Severe Unsolicited Adverse Events and Relationship to Study Vaccine

Severe Unsolicited AEs were reviewed according to vaccine relatedness and treatment group. The ISR summary tables Table 14.3.1.2 Module 5, Volume 19, pp180-210, and the electronic datasets revealed 61 severe AEs occurring in 40 subjects, 24 severe AEs in 17 Flublok recipients and 37 events in 23 placebo recipients. The CSR (Table 14.3.1.10, pp444-454 and datasets) revealed a total of 100 severe AEs occurring in 67 subjects, 44 severe AEs in 29 (1.2%) Flublok recipients and 56 events in 38 (1.6%) placebo recipients. Of the total severe AEs, 12 events (in 1 Flublok and 2 placebo recipients) were considered related or possibly related (Table 14):

Table 14 Related or Possibly Related Severe Unsolicited AEs – Safety Population – PSC04

Subject ID	Group	Preferred term	Time to onset (days)*	Causality	Tx	Outcome
13-09654-b(6)	FB	Headache	17	Possibly Related	Med	Resolved without sequelae
13-09654-b(6)	FB	Insomnia	14	Possibly Related	Med	Ongoing
13-09654-b(6)	FB	Pharyngolaryngeal pain	17	Possibly Related	None	Ongoing
19-14646-b(6)	P	Arthralgia	8	Related	None	Resolved without sequelae
19-14646-b(6)	P	Chills	8	Related	None	Resolved without sequelae
19-14646-b(6)	P	Fatigue	8	Related	None	Resolved without sequelae
19-14646-b(6)	P	Headache	8	Related	None	Resolved without sequelae
19-14646-b(6)	P	Injection site pain	8	Related	None	Resolved without sequelae
19-14646-b(6)	P	Nausea	8	Related	None	Resolved without sequelae
25-19381-b(6)	P	Headache	8	Related	Med	Ongoing
25-19381-b(6)	P	Photophobia	5	Related	None	Ongoing
25-19447-b(6)	P	Headache	8	Possibly Related	None	Resolved without sequelae

FB=Flublok; P=Placebo; Tx=treatment given; Med=medication given

*Time from vaccination to onset of AE in days

Source: CR Vol 2 Table 14.3.1.10, pp444-454.

The remaining 88 events involved 63 subjects and were assessed as not related to the study vaccines. Twenty-eight of these 63 subjects were Flublok recipients. After review of all case narratives, the following case merited further consideration:

- Case summary: Dizziness, Facial Swelling, Facial Pain, Nausea, and Pruritis. Subject 16-12074-b(6)--- is a 35 year old African American female who developed dizziness, nausea, itching of the arms and legs, and pain and swelling of the face 16 days after vaccination with Flublok. All symptoms were graded as severe in intensity but non-serious. Past medical history was unremarkable. Allergies included Loestrin and Bactim. No concomitant medications reported during the study other than multivitamins since December 2005. She experienced Grade 1 local pain on September 17, 2007 (Day 0, vaccination), then no complaints until October 3, 2007 (Day 16) when she reported severe dizziness, swollen lips, itchy palms and posterior thighs, nausea, and pain in her face. She saw her personal physician on October 3, 2007. Copy of the exam record noted red puffy eyes and a puffy upper lip. The vaccination site was unremarkable and there were no other abnormal signs. Copies of laboratory work reveal unremarkable hematology and chemistries. The sedimentation rate was slightly elevated 34 (normal 0-20). She required no specific treatment. The

events were assessed by the Investigator as not related to the study vaccine, and they resolved without sequelae.

Reviewer comment: This description suggests a mild hypersensitivity event in a subject with a history of drug allergies. The onset of symptoms 16 days following vaccination suggest that these findings probably were not related to Flublok. However, hypersensitivity reactions will be monitored in future trials and as part of the PVP.

There were 3 reports of diarrhea, migraine, and pharyngolaryngeal pain in different subjects that occurred 4 to 10 days following vaccination with Flublok. These were assessed as not related to the vaccine. These events are not unusual and all resolved without sequelae.

The remaining 25 subjects with severe AEs that were assessed as not related had events that did not appear to be related to Flublok based either on the absence of a strong temporal relationship or a lack of biologic plausibility.

Reviewer comment: Overall, there were slightly more placebo recipients (1.6%) than Flublok recipients (1.2%) who experienced severe AEs. No unusual trends or imbalances are apparent.

Events that Occurred in Fewer than 0.5% of Subjects but of Potential Interest

Datasets were examined for autoimmune or hypersensitivity phenomena, and for idiosyncratic reactions that have been reported following immunization with a variety of vaccines.

Review of nervous system disorders, blood and lymphatic system disorders and musculoskeletal and connective tissue disorders revealed only rare reports of incidents, with a balance between reports in Flublok and placebo recipients. Among the Flublok recipients, one event was serious and a few were severe, however, these few events in particular and the majority of these events of potential interest in general were assessed by the investigators as not related to Flublok.

Reviewer comment: After evaluating the datasets, CRFs, and selected case narratives of subjects who reported the selected events in these System Organ Class categories, the reviewer concurs that none of the events of interest appeared related to Flublok.

In light of the theoretical concern regarding hypersensitivity reactions possibly associated with this insect cell culture-derived influenza vaccine, particular attention was paid to reports of immune system disorders (including hypersensitivity) and skin and subcutaneous disorders (including rashes).

Immune System Disorders are presented in Table 15:

Table 15 - Immune System Disorders – PSC04

Unsolicited AE by MedDRA PT, n(%)	Flublok N=2344	Placebo N=2304
Hypersensitivity	3 (0.12)	1 (0.04)
SAE	0	0
Severe	0	0
Related	1	0
Seasonal allergy	7 (0.3)	9 (0.4)

Source: Electronic datasets.

- Of 4,648 subjects, 20 experienced immune system disorders. Four were categorized as hypersensitivity events and the remainder as seasonal or pet allergies.
- **Hypersensitivity:** Three Flublok recipients and 1 placebo recipient experienced hypersensitivity reactions. Two of the three Flublok events (13-09668- b(6) and 24-18902- b(6)) were considered mild and not related to the study vaccine by the investigator, but were ongoing at Day 28 of the study. The third subject (25-19731- b(6)) had a moderate hypersensitivity event classified as possibly related to study vaccine, but which resolved without sequelae. The subject who received placebo had a moderate event that was assessed as not related. Case narratives and the CRFs for the Flublok subjects were provided by the Applicant. Upon review, only one appears to have had a hypersensitivity reaction possibly related to Flublok to this reviewer:
 - Subject 25-19731- b(6)--is a 22 year old white non-Hispanic female who was vaccinated with Flublok on October 12, 2007. PMH included seasonal allergic rhinitis in 2003, exercise-induced symptoms (bronchiolar constriction, facial edema, edema of extremities, rash, itchiness, and swelling of the tongue) in 2005, and mild asthma and headaches. She reported Grade 2 redness at the injection site on Day 0 and abrupt onset of swollen lips and tongue 10 hours and 20 minutes following vaccination. She self-medicated with loratidine 10mg and Benadryl 25mg, and the symptoms resolved by Study Day 2. The Investigator assessed this event as moderate and possibly related to the study vaccine.

Reviewer comment: This subject had a history of atopy and, while it is possible that she reacted to an unidentified allergen to which she was exposed in the 10 hour interval between vaccination and onset of symptoms, Flublok cannot be excluded as the cause of her hypersensitivity reaction. Hypersensitivity reactions are known to occur following influenza vaccination. A warning will appear in Section 4, Contraindications, of the product label and hypersensitivity reactions will continue to be monitored in future trials and as part of the PVP. The other two cases of “hypersensitivity” appear to be cases of allergic rhinitis and/or nasopharyngitis rather than hypersensitivity to Flublok.

Skin and Subcutaneous Tissue Disorders are presented in Table 16:

Table 16 Skin and Subcutaneous Tissue Disorders – PSC04

Unsolicited AE by MedDRA PT, n(%)	Flublok n=2344	Placebo n=2304
Rash/rash pruritic	4 (0.17)	1 (0.04)
SAE	0	0
Severe	0	0
Related	1	0
Swelling face	1 (0.04)	0
SAE	0	0
Severe	1	0
Related	0	0

Source: electronic datasets

- **Rash/rash pruritic:** Four Flublok and one placebo subject experienced rash. One Flublok subject had a moderate intensity rash assessed as possibly related to the study vaccine, but that resolved without sequelae. The remainder were mild, non-serious, and assessed as not related to study vaccines. Table 17 was derived from the electronic datasets:

Table 17 Rash Following Flublok – PSC04

Subject	Onset after vax (days)	Severity	Causality	Outcome
12-08876- b(6)	1	Mild	Not Related	Resolved
13-09825- b(6)	27	Mild	Not Related	Resolved
16-12140- b(6)	4	Mild	Not Related	Resolved
16-12475- b(6)	2	Moderate	Possibly Related	Resolved

Source: electronic datasets

Reviewer comment: *These subjects were different from those who were reported as having hypersensitivity reactions. CRFs and case narratives were provided by the Applicant and reviewed:*

- Subject 12-08876- b(6) is a 33 year old Korean male, no reported PMH or medications. He was vaccinated (left deltoid) with Flublok on September 25, 2007. On Days 1-3, he reported mild pruritis, region not specified, which required no treatment and which resolved without sequelae. On Days 1-2, he experienced rash in the lower arm pit area (side not specified), described as mild and resolved without treatment or sequelae. The event was assessed by the Investigator as not related to the study vaccine.
- Subject 13-09825- b(6) is a 22 year old Korean male whose PMH was not recorded on the electronic CRF (pending from site). He was vaccinated with Flublok on September 20, 2007 and on October 17-24, 2007 (Days 27-34), experienced an upper respiratory infection (URI) and itchy rash over the back and chest. The rash was described as mild, required no treatment, and resolved without sequelae. The subject had taken DayQuil (Anilides) and Robitussin (guaifenesin) for the URI, but the rash began before these medications were

started. The event was assessed by the Investigator as not related to the study vaccine.

- Subject 16-12140- b(6) is an 18 year old African American female who was vaccinated with Flublok on September 18, 2007. She reported no PMH or medications. On Day 4 she reported an itchy rash over her back. The rash was described as mild, required no treatment, and resolved without sequelae. In retrospect, on June 11, 2008, the clinical site re-classified the event from being “not related” to “possibly related” to the study drug.
- Subject 16-12475- b(6)--- is a 34 year old female who was vaccinated with Flublok on September 19, 2007. PMH included seasonal allergies and allergy to “mycins”. On Days 2-4 she experienced left leg and back bruising, felt not related to the vaccine, and rash on the face, neck, chest and shoulder. The rash was described as moderate, required no treatment, and resolved without sequelae. The rash was assessed as possibly related to the study vaccine because of the temporal relationship between vaccination and onset.

Reviewer comment: In three of the four cases of rash, one cannot exclude a relationship to vaccination with Flublok because of a temporal relationship. Rash will be monitored in postmarketing studies.

- **Swelling face:** Subject 16-12074- b(6), a Flublok recipient, experienced severe, but not serious, facial swelling, onset 16 days after vaccination, probably not related. Please see the summary of the CRF and case narrative provided by the Applicant in the preceding review of severe AEs.

Oculorespiratory Syndrome (ORS): Search of the datasets for the terms “conjunctivitis” and “red eyes” yielded only one Flublok recipient, #04-02471- b(6)---, who reported conjunctivitis and no other symptoms, 21 days post-vaccination. This event was not suggestive of ORS. No Fluzone recipients reported conjunctivitis in this study.

Pregnancies – CSR

Thirty-seven (1%) of 2740 female subjects in PSC04 became pregnant during the study, 20 had received Flublok and 17 had received Placebo. Complete follow-up was available for 15 (75%) Flublok recipients and for 15 (88%) placebo recipients. Ten pregnancies in the Flublok group and 8 in the placebo group were uneventful and resulted in normal term births. Two Flublok recipients experienced pregnancy-related AEs but delivered healthy infants. There were one spontaneous abortion and two elective terminations in the Flublok group. Among the placebo recipients, there were 3 SAEs, 1 spontaneous abortion, 1 ectopic pregnancy, and 3 elective terminations.

Reviewer comment: Case narratives were reviewed. The reviewer concurs with the investigators’ assessments that the events were unrelated to receipt of Flublok.

Reviewer comment: The Applicant states that they were unable to obtain follow-up of 25% of pregnancies that occurred in Flublok recipients despite phone calls and

certified mail. However, among those for whom data were available, there did not appear to be vaccine-related AEs nor an imbalance between treatment groups.

Unsolicited Adverse Events

Table 18 summarizes all Unsolicited AE's that occurred from Day 0 through Day 28 in at least 0.5% of subjects regardless of relationship to the Study Vaccine. Events are categorized according to MedDRA PT and SOC.

Table 18 Unsolicited Events by System Organ Class and Preferred Term Occurring in ≥ 0.5% of Subjects in either Treatment Group – Safety Population PSC04

System Organ Class Preferred Term	Flublok (N=2344)		Placebo (N=2304)	
	n (%)	E	n (%)	E
Subjects with at least one AE	400 (17)		384 (17)	
Gastrointestinal disorders	49 (2.0)	63	48 (2.1)	61
Diarrhea	13 (0.6)	14	14 (0.6)	14
Nausea	13 (0.6)	13	13 (0.6)	13
General disorders and Administration site Conditions	45 (1.9)	57	47 (2.0)	67
Fatigue	13 (0.6)	13	22 (1.0)	23
Pyrexia	16 (0.7)	16	9 (0.4)	10
Infections and Infestations	101 (4.3)	110	103 (4.5)	107
Nasopharyngitis	15 (0.6)	15	23 (1.0)	23
Sinusitis	12 (0.5)	12	13 (0.6)	13
URI	18 (0.8)	18	24 (1.0)	24
Injury, poisoning, and Procedural complications	30 (1.3)	31	18 (0.8)	19
Musculoskeletal and Connective tissue ds	31 (1.3)	36	36 (1.6)	40
Arthralgia	6 (0.2)	6	11 (0.5)	11
Myalgia	8 (0.3)	8	7 (0.3)	7
Nervous system disorder	58 (2.5)	59	57 (2.5)	60
Headache	35 (1.5)	35	43 (1.8)	44
Respiratory, thoracic, and mediastinal disorders	130 (5.5)	201	116 (5.0)	173
Cough	49 (2.1)	49	37 (1.6)	37
Nasal congestion	37 (1.6)	39	31 (1.3)	32
Pharyngolaryngeal pain	42 (1.8)	42	49 (2.1)	49
Rhinorrhea	30 (1.3)	30	27 (1.2)	28
Skin and subcutaneous Disorders	16 (0.7)	18	16 (0.7)	18

n = number of subjects

% = percentage of subjects experiencing a particular AE

E = number of events occurring in a specific category and treatment group, derived from the datasets

URI = upper respiratory tract infection

Bold font indicates SOC category and treatment groups.

Source: Applicant's Tables 14.3.1.1, CR, Vol 2, pp276-285, and review of the electronic datasets.

- Cough was the most frequent unsolicited AE reported by Flublok recipients (2.1%), followed by pharyngolaryngeal pain (1.8%), nasal congestion (1.6%), and headache (1.5%).
- Fever, or pyrexia, occurred almost twice as frequently in the Flublok group as compared to placebo but the rate was still <1% (0.7% vs (0.4%). The frequencies of other events as reported by the Applicant were low and were very similar between the Flublok and placebo groups.

Reviewer comment: Evaluation of the electronic datasets indicated that the number of subjects experiencing AEs in each preferred term and system organ class category were nearly identical to the Applicant's report.

Unsolicited AEs according to Severity and Relationship to Study Vaccine

- For each Unsolicited AE, as categorized by MedDRA PT, the Applicant reported most as being mild or moderate in severity, and as being unrelated to the Study Vaccines.
- Seventeen percent of subjects in both the Flublok and the placebo groups experienced one or more Unsolicited AEs of any type. The severity profile was very similar for both groups with the majority of events in the Flublok group being either mild (64%) or moderate (29%). Most events were considered not related to Flublok (84%) or placebo (82%). There were two deaths, one in each treatment group.

Reviewer comment: There were relatively small differences between the Applicant's number of subjects experiencing events and the reviewer's numbers extracted from the datasets. For purposes of the review, the Applicant's numbers will be used because the differences were relatively small and observed only in lower severity categories.

- An assessment of Unsolicited AEs from Day 0 to Day 28 according to lot assignment and categorized according to SOC, PT and severity grade did not reveal significant differences in the frequency or severity of Unsolicited AEs according to lot.

Unsolicited Adverse Events by System Organ Class

- The reviewer compared the Applicant's report of subjects with Unsolicited AEs by SOC to the Medical Officer's results from review of the electronic datasets (data not shown).

Reviewer comment: Overall, the number of subjects experiencing AEs as categorized by SOC was very similar between the two treatment groups. The numbers reported by the Applicant were nearly identical to the reviewer's results derived from the electronic datasets.

Eight Day Solicited Reactogenicity Events (Day 0-Day 7)

- Eight day solicited reactogenicity events (Day 0 – Day 7) were assessed in the Safety Population: N = 4648: 2344 Flublok recipients and 2304 placebo recipients. At least one reactogenicity event overall was reported by 53% of the Flublok recipients as opposed to 33% of the placebo group. The majority of subjects did not experience local reactions. Most reactions were mild in intensity, very few were severe. The most common local reaction in the Flublok group was pain at the injection site. Flublok recipients experienced significantly more pain at the injection site (37.4%) than did the placebo group (8.1%). The most frequent solicited systemic events experienced by Flublok recipients were headache (15.4%), fatigue (15.0%), and myalgias (10.5%). The majority of these events were mild in intensity. Overall, the frequency of systemic reactogenicity events was similar between the two groups.
- Table 19 presents solicited reactogenicity events through Day 7 according to treatment group and severity. Data is shown for all events (mild, moderate and severe) and severe events within each category. The tables are based on the Applicant's Tables 14.3.6.1 and 14.3.6.7, Module 5, Volume 19, pp 396-414, and also compare the Applicant's data as reported in the paper submission with data derived from the electronic datasets that accompanied the original BLA submission.

Table 19 Solicited Local and Systemic Reactogenicity Events Reported between Day 0 and Day 8 Post-vaccination, Flublok vs. Placebo, According to Severity – Safety Population – PSC04

Parameter	Treatment	Flublok Dataset N=2344	Flublok Applicant n=2344	Placebo Dataset n=2304	Placebo Applicant n=2304
Solicited AE	Severity Grade*	n	n (%)	N	n (%)
Total # with any reaction (%)	Any grade 1, 2, 3	Nd	1198 (53)	Nd	727 (33)
Injection site pain	Any grade 1, 2, 3	885	851 (37.4)	182	181 (8.1)
Injection site pain	Severe (3)	2	2 (<0.1)	1	1 (0.04)
Injection site bruising	Any grade 1, 2, 3	79	75 (3.3)	58	59 (2.6)
Injection site bruising	Severe	1	1 (0.04)	1	1 (0.04)
Measured redness	Any grade 1, 2, 3	102	91 (4.0)	50	47 (2.1)
Measured redness	Severe	4	4 (0.2)	1	1 (0.04)
Measured swelling	Any grade 1, 2, 3	92	77 (3.4)	44	42 (1.9)
Measured swelling	Severe	6	6 (0.3)	2	2 (0.08)
Fever	Any Grade 1, 2, 3	19	17 (0.8)	14	12 (0.5)
Fever	Severe	4	4 (0.2)	1	1 (0.04)
Fatigue	Any grade 1, 2, 3	391	340 (15.0)	380	333 (14.9)
Fatigue	Severe	12	12 (0.5)	11	11 (0.5)
Shivering, chills	Any grade 1, 2, 3	76	70 (3.0)	77	71 (3.2)
Shivering, chills	Severe	6	6 (0.3)	4	4 (0.2)
Joint pain	Any grade 1, 2, 3	99	89 (3.9)	90	83 (3.7)
Joint pain	Severe	6	6 (0.3)	4	4 (0.2)
Muscle pain	Any grade 1, 2, 3	262	239 (10.5)	173	154 (6.9)
Muscle pain	Severe	6	6 (0.3)	8	8 (0.4)
Headache	Any grade 1, 2, 3	394	349 (15.4)	391	354 (15.9)
Headache	Severe	15	15 (0.2)	13	13 (0.6)
Nausea	Any grade 1, 2, 3	146	129 (5.7)	126	109 (4.9)

Parameter	Treatment	Flublok Dataset N=2344	Flublok Applicant n=2344	Placebo Dataset n=2304	Placebo Applicant n=2304
Solicited AE	Severity Grade*	n	n (%)	N	n (%)
Nausea	Severe	6	6 (0.3)	10	10 (0.4)

n = number of subjects in treatment group

E = number of events for each reactogenicity category derived by review of the electronic datasets.

Applicant states that subjects with multiple symptoms in the same category were counted once per category using the symptom with the maximum grade.

*Grade 0: no symptoms, or, for injection sites, measures less than 10mm

Grade 1 (mild): noticed it, but it didn't interfere with usual activities at all

Grade 2 (moderate): had it, and it was bad enough to prevent a significant part of usual activities

Grade 3 (severe): had it, and it prevented most or all of normal activities, or had to see a doctor for prescription medicine.

Fever: mild= $\geq 100.4^{\circ}$ to $< 101.1^{\circ}$ F; moderate= $\geq 101.2^{\circ}$ to $< 102.2^{\circ}$ F; severe= $\geq 102.2^{\circ}$ F

**The Applicant indicates that the data do not include missing values, so that the number of subjects in each AE category may not add up to the total number of subjects in that treatment group. The number of missing subject data for each AE category was calculated by subtracting the total number of subjects who reported grade 0 through 3 AEs from the total treatment group N. For all categories except fever, the number of subjects with missing values was 72 in the Flublok group and 73 in the placebo group so that these denominators are 2272 and 2231 respectively. For fever, 89 Flublok recipients and 104 placebo recipients were missing data, making these denominators 2255 and 2200 respectively.

nd = not determined

Reviewer comment: The reviewer compared the Applicant's numbers with data derived from the source electronic datasets. As the reviewer's assessment did not identify important differences, the Applicant's reported numbers will be used.

Reactogenicity events by Lot:

Because of the failure to demonstrate lot consistency for the H3 antigen, the Applicant conducted an exploratory analysis of reactogenicity events according to lot.

Reviewer comment: The rate of reactogenicity events, including Grade 3 events, was similar for all three lots, and did not appear to be influenced by the higher A/Wisconsin (H3) antigen content of Lot A relative to Lots B and C (data not shown).

CRFs reviewed for study PSC04

CRFs for specific subjects of interest are reviewed and referenced in the relevant sections of Section 8.1.1.2.3 Safety Outcomes.

Discontinuations Due to Adverse Events

Nine subjects discontinued the study due to AEs; 5 Flublok and 4 placebo recipients. In addition, there were 2 deaths, one in each treatment group. The majority of discontinuations were due to pregnancy. Discontinuations are summarized in Table 20.

Table 20 Discontinuations Due to AEs or Death – CSR – PSC04

Treatment	Subject	Disposition	Reason for discontinuation
Flublok	04-02568	Death	Pulmonary embolism/death
Flublok	05-03321	AE	Pleuropericardial effusion
Flublok	19-14659	AE	Pregnancy
Flublok	19-14567	AE	Pregnancy
Flublok	19-14509	Other	Pregnancy
Flublok	17-10859	Withdrew	Pregnancy
Placebo	05-03291	Death	MVA/death
Placebo	11-08096	AE	Multiple fractures
Placebo	15-11410	AE	Pregnancy
Placebo	19-14587	AE	Pregnancy
Placebo	08-05715	Other	Pregnancy

Source: Table 35, CR Vol 2, Sect12.5.4, p 148 and Table 14.1.1, CR Vol 2, p158

Reviewer comment: Discontinuations due to AEs or death are evenly balanced between treatment arms and do not introduce bias into the overall analyses of the study data.

Vital Signs

There were no unexpected treatment emergent trends or patterns in vital signs identified following Flublok administration in study PSC04 other than a trend toward more fever in the 8 days following vaccination among Flublok recipients.

Laboratory Evaluation

No clinical laboratories were performed for this study other than screening urine pregnancy tests. Pregnancies are discussed in Section 8.1.1.2.3.

8.1.1.3 Comments Study PSC04: Safety Conclusions

- One death occurred in each treatment group; neither appeared related to the vaccines. Discontinuations due to AEs were similar and, aside from the 2 deaths, were due primarily to pregnancy (Flublok = 4, placebo = 3). Only one Flublok recipient was discontinued due to a possible vaccine-related AE (pleuropericarditis). Of 30 Flublok and 35 placebo recipients who experienced SAEs, only one appeared possibly related to Flublok, the same case of pleuropericarditis. This subject developed pleuropericarditis within 11 days of receiving Flublok, and an idiosyncratic or immune-mediated hypersensitivity reaction cannot be excluded. Although this would be an unusual reaction to traditional trivalent influenza vaccines, Flublok is manufactured in a novel insect cell system, and hypersensitivity reactions should be monitored in future trials and as part of the Pharmacovigilance Plan. This event will be described in the product labeling, Adverse Events Observed in Clinical Studies Section 6.1.
- Although low in frequency, there were more cases of hypersensitivity reactions reported for Flublok recipients, n=3, (0.17%) than for placebo, n=1, (0.04%). Review of the CRFs and case narratives revealed that 2 of the Flublok hypersensitivity reactions (0.08%) were possibly related to the vaccine. One case was severe and included facial swelling, facial pain, pruritis, nausea and dizziness; this occurred 16 days post-vaccination making causality unlikely. The second case was characterized as abrupt onset of moderate swelling of the lips and tongue 10 hours post-vaccination,

making causality more likely. In addition to these hypersensitivity reactions, there were more cases of skin rash reported among Flublok recipients, n=4 (0.17%), than for the placebo group, n=1 (0.04%). Review of the CRFs and case narratives revealed that three of the Flublok cases (0.17%) were possibly related to the vaccine. There were no cases suggestive of the Oculorespiratory Syndrome. Hypersensitivity reactions will be monitored in postmarketing studies.

- The VRBPAC expressed concern over the case of pleuropericarditis as a potential safety signal and recommended that additional safety data be required either pre-licensure or as a post-marketing requirement. This issue will be discussed further in Sections 10 and 12 (Overview of Safety and Conclusions Overall).
- Flublok recipients experienced more reactogenicity events overall than did placebo recipients, 53% vs. 33%, respectively. Pain at the injection site occurred significantly more often in the Flublok group (37.4%) than in the placebo group (8.1%). However, most events were mild and very few were severe in intensity. The frequencies of other reactogenicity events were similar between the two groups. Reactogenicity rates for Flublok were similar to those reported for traditional egg-grown TIVs. Despite the different quantities of rHA antigen and protein among the three lots of H3 A/Wisconsin and the failure to demonstrate lot consistency, the frequencies of reactogenicity events among the three lots were similar.
- Seventeen percent of subjects in both treatment groups experienced Unsolicited AEs. Severity and vaccine relatedness were very similar between the Flublok and placebo groups. The majority of Flublok events were either mild (64%) or moderate (29%).
- Twenty Flublok subjects became pregnant after vaccination (range 24-107 days); 15 had complete follow-up. There were one spontaneous abortion and two elective terminations. The remaining 12 subjects for whom follow-up was available gave birth to normal term infants.

8.1.1.4 Comments Study PSC04: Efficacy and Safety Conclusions

- In summary, no unusual safety trends or patterns were noted. Because of the temporal relationship to vaccination, the case of pleuropericarditis may represent an adverse reaction to Flublok and a safety signal. Alternatively, the event might have been coincidental and consistent with echo- or coxsackievirus infection occurring in a young person in the late summer/early fall. The occurrence of this event and the 11% lost to follow-up after Day 28 for whom safety data are unknown, suggest the need for further postmarketing assessments of product safety.
- A single Flublok dose of 135mcg elicited immune responses that exceeded the co-secondary endpoint acceptance criteria. These data are somewhat limited by difficulties in interpreting HAI titers obtained using BEVS-derived antigens in the HAI assay because such titers are higher than those obtained with egg-derived antigens.
- The primary lot consistency endpoint was not met for the H3 strain, but this did not appear to impact clinical safety or efficacy endpoints. Subsequent to conducting study PSC04, FDA worked with PSC to refine –b(4)-----

formulation specifications to ensure consistent HA antigen content in the final trivalent vaccine going forward.

- Flublok also failed to meet the pre-specified clinical efficacy endpoints against antigenically similar virus strains. In an influenza season characterized by a predominance of antigenically mismatched strains, however, the vaccine efficacy of Flublok against culture-confirmed influenza illness due to all isolated virus strains was 44.8% (LB 95% CI 24.4%). Given these data, it is reasonable to expect that the VE for Flublok would be at least as good against antigenically similar virus strains.

8.1.2 Trial #2

8.1.2.1 Applicant's Protocol Number PSC06 (BB-IND 11951) "Evaluation of the Safety and Reactogenicity of Flublok, Trivalent Recombinant Baculovirus-Expressed Hemagglutinin Influenza Vaccine, and Comparison of the Immunogenicity, Efficacy and Effectiveness of Flublok to a Licensed Egg-Grown Influenza Vaccine in Adults Aged 50 to 64"

8.1.2.1.1 Objective/Rationale:

Primary Objectives:

- To evaluate the safety and reactogenicity of Flublok and a trivalent inactivated influenza vaccine licensed in the United States (TIV; Fluzone) in healthy adults age 50 to 64 years.
- To evaluate the immunogenicity of Flublok and TIV in the subject population according to the placebo-controlled criteria specified in CBER's May 2007 Guidance Document on Seasonal Influenza Vaccines.

Secondary Objectives:

- To compare the immunogenicity of Flublok and TIV in the subject population according to the non-inferiority criteria specified in CBER's May 2007 Guidance document on Seasonal Influenza Vaccines.
- To compare the relative efficacy and effectiveness of Flublok and TIV in subjects for (a) prevention of culture-positive CDC-ILI; and (b) culture-positive respiratory illness (regardless of whether the case definition for CDC-ILI is met) during the 2007-2008 influenza season. Only subjects from whom isolates were antigenically matched to the vaccine were included in the secondary efficacy endpoint analyses.

Exploratory Objectives:

- To compare the efficacy and effectiveness of Flu Blok and TIV in subjects for a) development of culture-positive CDC-ILI, regardless of antigenic relatedness of the isolate to the vaccine strains; and b) CDC-ILI regardless of culture results.

8.1.2.1.2 Design Overview

- PSC06 was a Phase 3, prospective, randomized, modified double-blind, active-controlled multi-center trial designed to evaluate the safety, reactogenicity,

immunogenicity, and efficacy of Flublok and Fluzone in healthy adults age 50 to 64 years.

- A total of 602 subjects were enrolled at 5 sites in the United States (California and Hawaii) prior to onset of the 2007-2008 influenza season. Subjects were stratified according to receipt of influenza vaccine during the 2006-2007 influenza season and then randomized 1:1 within the 2 strata to receive either Flublok or Fluzone.
- Subjects were vaccinated on Day 0. Reactogenicity events were recorded with the assistance of a Memory Aid from Day 0 to Day 7, and then collected via a telephone call 8-10 days following vaccination. Adverse events including reactogenicity events persisting after Day 7 were recorded as Unsolicited or Treatment-Emergent AEs, and were collected at Visit 2, Day 28. SAEs were collected on Day 28 and until the EOIS for an approximate total of 6 months. Serologies were collected prior to vaccination at Visit 1, Day 0 and at Visit 2, Day 28.
- Flu Surveillance Period: Subjects were instructed to call the clinic and return for an illness evaluation within 24-72 hours if, at any time during the study, they had a symptom score of 2 or more on their Flu Symptom Card. Active surveillance for influenza was to begin when 5% of isolates in the field were positive for influenza. Surveillance was to end when less than 20% of isolates were positive for influenza, a timepoint designated as the EOIS. Subjects were contacted by telephone bi-weekly during the influenza surveillance period. Those subjects who scored Flu Symptoms of 2 or more were evaluated at a Supplemental Illness visit in the clinic where nasal and throat swabs were obtained for influenza culture. At the EOIS, a final telephone contact was made to collect SAE information, concomitant medications, and to review the Flu Symptoms card.

Study Duration

- Active study period: 28 days.
- Total study duration until EOIS, approximately 6 months.
- First subject enrolled: September 25, 2007.
- Last subject completing Day 28 contact (Interim Study Period): December 19, 2007.
- Last subject completed: May 30, 2008.

Subject Stratification

- Subjects were stratified based on whether they received TIV during the 2006-2007 influenza season, then randomized 1:1 to receive Flublok or Fluzone using a block method. The investigators, Applicant, subjects and all staff members involved in study assessments were blinded to treatment assignment. A pharmacist was unblinded to the randomization code and prepared the vaccine for injection. The pharmacist or another unblinded staff member who was not involved in any study assessments administered the vaccine. No emergency unblinding occurred during the study.

8.1.2.1.3 Population

- The study population was to be composed of 600 healthy adults aged 50-64 from six Kaiser Permanente study sites who fulfilled eligibility criteria.
- Noteworthy exclusion criteria were similar to those in PSC04

8.1.2.1.4 Products Mandated by the Protocol

A 0.5mL dose of Flublok was administered once on Day 0 IM in the non-dominant deltoid muscle. Each dose contained a total of 135µg of rHA as determined by SRID, representing the three recommended strains of influenza virus for the 2007-2008 Northern Hemisphere influenza season:

- 45µg rHA A/Solomon Islands/03/2006 (H1N1)
- 45µg rHA A/Wisconsin/67/2005 (H3N2)
- 45µg rHA B/Malaysia/2506/2004 (B strain)

An equal number of three lots of Flublok were used in the study: Lot 50-07010; Lot 50-07011; and Lot 50-07014.

Reviewer comment: These are the same three lots as were used in study PSC04 which failed to demonstrate lot consistency for lot A to A/Wisconsin.

Fluzone, sanofi pasteur, 2007/2008 formulation, was the TIV comparator. Each 0.5ml dose contained a total of 45µg HA, the same antigens as contained in Flublok:

- 15µg rHA A/Solomon Islands/03/2006 (H1N1)
- 15µg rHA A/Wisconsin/67/2005 (H3N2)
- 15µg rHA B/Malaysia/2506/2004 (B strain)

Fluzone was provided in multi-dose vials from a single lot (U2463AA), and was injected as a 0.5mL dose IM in the non-dominant deltoid muscle of the arm.

8.1.2.1.5 Endpoints

Primary Safety Endpoints

- Frequency of Solicited reactogenicity events, Unsolicited and/or treatment-emergent AEs, and SAEs, solicited in the clinic, via memory aids, phone calls, and targeted physical exams when indicated.

Primary Immunogenicity Endpoints and Criteria for Success

- Seroconversion or 4-fold increase in HAI titer to at least 1:40
 - the LB of the 2-sided 95% CI must meet or exceed 40% for each of the three vaccine antigens.
- Proportion with post-vaccination HAI titer \geq 1:40 at Day 28
 - The lower bound of the 2-sided 95% CI should meet or exceed 70% for each of the three vaccine antigens.

Secondary Immunogenicity Endpoints and Criteria for Success: Non-Inferiority

- The upper bound (UB) of the 2-sided 95% CI of the GMT ratio (GMT_{US licensed TIV}/GMT_{Flublok}) 28 days post-vaccination should not exceed 1.5.
- The UB of the 2-sided 95% CI on the difference between the SCRs (SCR_{US licensed TIV} – SCR_{Flublok}) should not exceed 10%.

Secondary Efficacy/Effectiveness Endpoints and Criteria for Success

- Proportion of subjects in each vaccine group who experience culture-positive CDC-ILI during the 2007-2008 influenza season, and in whom the influenza isolates were antigenically similar to the strains included in the vaccine.
- Proportion of subjects in each vaccine group who experience culture-positive respiratory illness during the 2007-2008 influenza season, and in whom the influenza isolates were antigenically similar to the strains included in the vaccine.
- CDC-ILI was defined as fever of $\geq 100^{\circ}\text{F}$ oral accompanied by cough and/or sore throat on the same day or on consecutive days.

Exploratory Endpoints

- The proportion of subjects who experienced culture-confirmed CDC-ILI regardless of antigenic match to the vaccine strains.
- The proportion of subjects who developed CDC-ILI regardless of culture.

Reviewer comment: Comparison of the final study protocol and the Interim Clinical Study Report indicates that the pre-specified safety and immunogenicity endpoints were not modified following analysis of the data.

Validation of the HAI Assay: Please see Section 4.4 and discussion of the assay issues in study PSC04.

Reactogenicity (Solicited) Adverse Events: the frequency of local and systemic reactions for 8 days following vaccination (Day 0 through Day 7), noted on the subject Memory Aid and assessed on the Day 8 contact.

- Local (injection site) reactions included: local pain; bruising; discomfort; tenderness; measured erythema/redness; and measured induration/swelling (Grading scale same as for PSC04).

Reviewer comment: The original protocol for PSC06 planned to assess “discomfort” and “tenderness” rather than local pain or bruising (and in addition to redness and swelling). However, the sample Memory Aid/Reactogenicity Card and CRF actually captured local pain, bruising, redness and swelling. These were the same variables as were captured in PSC04.

- Systemic reactions included: fever ($\geq 100^{\circ}\text{F}$); fatigue/malaise; chills; joint ache; myalgia; headache; and nausea.
- Grading scale for fever:
 - Grade 1 (mild): ≥ 100 to $< 101.1^{\circ}\text{F}$
 - Grade 2 (moderate): ≥ 101.2 to $< 102.1^{\circ}\text{F}$
 - Grade 3 (severe): $\geq 102.2^{\circ}\text{F}$

Unsolicited Adverse Events: The frequency of unsolicited and/or treatment-emergent AEs that occurred in the 28-day period following vaccination, as assessed on the Day 28 clinic visit or telephone call. Reactogenicity events that persisted beyond Day 7 were

recorded as Unsolicited/Treatment-emergent events AEs. Pregnancies were to be recorded as AEs.

- The site investigator was to evaluate all AEs for severity and relationship to the study vaccine, report action taken, and follow until clinically resolved or stable.
- Similar to PSC04, the NCI Common Terminology Criteria for Adverse Events (CTCAE) toxicity grading scale was used to grade AEs (see Section 8.1.1.1.5 for details of the grading scale).
- AEs were assessed as not related, possibly related or related to vaccine.
- All AEs and SAEs were classified by body system and PT using the Medical Dictionary for Regulatory Activities (MedDRA) as in PSC04.

Serious Adverse Events: All SAEs possibly related to the study vaccine were to be reported to the Applicant, Institutional Review Board (IRB), and to FDA. SAEs collected through Day 28 were included in the ISR; SAE's collected through the EOIS, 6 months, were included in the CSR.

8.1.2.1.6 Surveillance Monitoring

- All subjects were observed for at least 15 minutes immediately following vaccination and were contacted by telephone on Day 8 by study personnel to solicit reactogenicity symptoms for Day 0 to Day 7 of the Memory Aid. AE and concomitant medication information from these contacts were recorded by study personnel on the CRF. At the Day 28 serology visit, subjects also had a medical history review and a targeted physical exam if indicated. Changes in health status, concomitant medications, and AEs were reviewed and recorded.
- Follow/up Phone Calls/Flu Surveillance
 - During the flu-surveillance period, influenza illness was monitored actively and passively (see Design Overview, Section 8.1.2.1.2). Subjects who reported an influenza symptom score of 2 or greater on the Flu Symptoms Card were to have an illness evaluation in the clinic within 24-72 hours.
 - Flu symptom scoring was the same as for PSC04 (Section 8.1.1.1.6).
- During active bi-weekly surveillance calls, changes in health status and SAEs were also solicited.

Reviewer comment: *The flu symptoms assessment (definition of ILI) was identical to that used in study PSC04.*

- Influenza Illness Evaluations included an interval medical history and physical exam. NS/TS were to be obtained for viral culture.
- End of Study Evaluation/EOIS: At the EOIS a final phone call was to be made to record SAEs, any other change in health status, concomitant medications, and to review the Flu Symptoms Card.

Reviewer comment: *Sample Reactogenicity Memory Aid, Flu Symptoms Card, Case Report Form, Day 8 Telephone Assessment Card, and End of Study Record Card were reviewed and appeared appropriate.*

- AE and SAE Follow-up: The site investigator was to evaluate all AEs as to severity and relationship to the study vaccine, report action taken, and follow until clinically resolved or stable.
- Pregnancies: All pregnancies occurring during the study were to be reported as an AE. Each pregnancy was to be followed to term, and the Investigator was to record a narrative describing its course and outcome.

8.1.2.1.7 Statistical Considerations

- Please see the statistical review.
- Randomization and Blinding: please see 8.1.2.1.2 Design Overview.
- Analysis Population for Safety (Safety Population): all randomized subjects who received any dose of study medication were included in all safety analyses.
- Analysis Population for Immunogenicity (Evaluable Population): all randomized subjects that received the correct dose of vaccine and had titers taken at baseline and at Day 28 were included in the immunogenicity analyses. Subjects were analyzed according to treatment actually received.
- Subjects who withdrew or who were terminated were not replaced.
- Missing data were not imputed.
- Summary statistics were used to describe subject disposition, demographic data, and safety data.
- The Interim Analysis of safety and immunogenicity data through Day 28 was conducted by an independent statistician. The Applicant reported that personnel from the study sites, the Applicant, and the CRO who were directly involved in conducting the study remained blinded. Data collected after Day 28 was reported in the CSR as part of the final analysis at the conclusion of the study after the database was locked.
- Immunogenicity Analysis: Please see Section 8.1.2.1.5 for a description of the pre-specified Primary and Secondary Immunogenicity Endpoints.
- The frequencies and severity of AEs were reported according to MedDRA SOC and PT. Relationship to the study vaccine was reported by treatment group.
- Subjects with missing data from any particular analysis were excluded from the denominator. Sensitivity analyses were performed for selected AEs that had missing severity information, and in these cases the AE severity was assumed to be severe. Any AEs with a missing relationship assessment were assumed to be related to study vaccine.
- Sample Size: To demonstrate that Flublok could meet two co-primary endpoints for three vaccine antigens with an overall power of 80%, each of the six individual comparisons were constructed with a 2-sided α level of 0.05 and an individual power of 96.34%. Assuming a 5% dropout rate, the sample size determined for each treatment group was 300 subjects.
- Immune Response Hypotheses
 - Ho: the LB on the 95% CI for the SCR/4-fold rise in HAI titer 28 days post-vaccination will be $< 40\%$.
 - Ha: the LB on the 95% CI for the SCR/4-fold rise in HAI titer 28 days post-vaccination will be $\geq 40\%$.

- Ho: the LB on the 95% CI for the proportion with HAI titer $\geq 1:40$ 28 days post-vaccination will be $< 70\%$.
- Ha: the LB on the 95% CI for the proportion with HAI titer $\geq 1:40$ 28 days post-vaccination will be $\geq 70\%$.
- Non-inferiority hypotheses
 - Ho: UB of 95% CI on $\text{GMT}_{\text{Fluzone}}/\text{GMT}_{\text{Flublok}} \geq 1.5$
 - Ha: UB of 95% CI on $\text{GMT}_{\text{Fluzone}}/\text{GMT}_{\text{Flublok}} < 1.5$
 - Ho: UB of 95% CI for $(\text{SCR}_{\text{Fluzone}} - \text{SCR}_{\text{Flublok}}) \geq 0.1$
 - Ha: UB of 95% CI for $(\text{SCR}_{\text{Fluzone}} - \text{SCR}_{\text{Flublok}}) < 0.1$

Reviewer comment: For further discussion of the adequacy of the sample size and power of the study, please see the statistical review.

- Changes in the conduct of the study or planned analyses
 - EOIS immunogenicity data – After completion of the study, the Applicant reported that an error was discovered in the SAP, Section 5.2, p11, version 6. Secondary Endpoints erroneously stated that GMTs, SCRs, and proportion of subjects with HAI titers $\geq 1:40$ would be evaluated at the EOIS. However, according to the Applicant, these analyses were not intended and serologies were not collected or analyzed at this timepoint.

8.1.2.2 Results Study PSC06

8.1.2.2.1 Populations enrolled and analyzed

Subject Disposition and Protocol Deviations

Subject disposition and protocol deviations are presented in Table 21.

Table 21 Subject Disposition through EOIS – PSC06

Disposition	Flublok n (%)	Fluzone n (%)	Overall n (%)
Enrolled	300 (49.8)	302 (50.2)	602 (100)
Randomized	300 (49.8)	302 (50.2)	602 (100)
Vaccinated	300 (49.8)	302 (50.2)	602 (100)
Safety Population	300 (49.8)	302 (50.2)	602 (100)
Evaluable Population	299	302	601
Discontinued	1	2	3
-Death	0	0	0
-Due to AE	0	0	0
-Lost to follow-up*	0	1	1
-Withdrew consent*	1	1	2
-Randomized not Vaccinated	0	0	0
-Other	0	0	0
Deviations	--	--	7
-Blood collected outside of window	2	4	6
-Day 0 serology missing *	1		1
-ILI visit outside of window	0	1	1

Disposition	Flublok n (%)	Fluzone n (%)	Overall n (%)
-Reporting flu sx outside of window; -No NS/TS	2	5	7
-No NS/TS; reported sx w/in 72 hrs	1	2	3
Completed	298	300	598

*did not complete study

Source: Module 5, CR Volume 3, pp47-48, 50, and reviewer's
evaluation of the electronic datasets

Reviewer comment: *There were no deaths or discontinuations due to AEs. There were a total of 7 protocol deviations. One subject did not have the Day 0 serology recorded. Six subjects had the Day 28 serology drawn outside the window of Days 24-32. These serologies were collected on Day 23 or Days 33-61, and, because this deviation was not expected to have a significant impact on the HAI titer results, these six subjects were included in the Evaluable Population and immunogenicity analyses.*

Demographics

The demographic characteristics of the safety population of Study PSC06 are presented in Table 22.

Table 22 Demographics - Safety Population – PSC06

Parameter	Characteristic	Flublok n=300 (%)	Fluzone n=302 (%)	Overall n=602 %	US 2007 Census Data %
Race/ethnicity	White/ Caucasian	218 (73)	211 (70)	429 (71)	81.3
Race/ethnicity	Black/ African- American	12 (4)	9 (3)	21 (3)	13.0
Race/ethnicity	Latino/Hispanic*	23 (8)	29 (10)	52 (9)	7.4
Race/ethnicity	Asian	36 (12)	40 (13)	76 (13)	4.5
Race/ethnicity	American Indian/ Alaska Native	0	0	0	1.0
Race/ethnicity	Hawaiian/ Pacific Islander	1 (<1)	2 (<1)	3 (<1)	0.2
Race/ethnicity	Other	10 (3)	11 (4)	21 (3)	6.6
Gender	Male	113 (38)	110 (36)	223 (37)	n/a
Gender	Female	187 (62)	192 (64)	379 (63)	n/a
Age (years)	Mean	55.9	55.7	55.8	n/a
Age (years)	Median	56.0	55.0	56.0	n/a
Age (years)	Range	50-64	50-64	50-64	n/a

*Race and Hispanic origin are considered two separate concepts. The US Census Bureau in 2000 considered Hispanic or Latino as persons of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin regardless of race. Persons were first asked whether they considered themselves Hispanic or non-Hispanic, and were then asked what they considered to be their race.

Source: Table 14.1.3, Module 5, Volume 26, p78, review of the electronic datasets and on United States Census data for the year 2000

Reviewer comment: *Race/ethnicity, gender and age were similar between the two treatment groups. This study was conducted in California and Hawaii, and there was relative under representation of African-Americans and over representation of Asians when compared to the general US population.*

Influenza History

The proportion of subjects in each treatment group who reported having received influenza vaccination in the 2006-2007 season is presented in Table 23.

Table 23 Influenza History by Treatment Group – Safety Population – PSC06

Influenza vaccination status 2006/2007	Flublok n=300 (%)	Fluzone n=302 (%)
Yes	208 (69.3%)	210 (69.5%)
No	92 (30.7%)	92 (30.5%)
Total	300	302

Source: Review of electronic datasets

Reviewer comment: *The proportion of subjects who received influenza vaccination in the season preceding the study was almost identical in both treatment groups, with approximately two thirds of subjects reporting vaccination in 2006/2007.*

Past Medical History (PMH)

The PMH of subjects enrolled in Study PSC06 is presented in Table 24.

Table 24 Past Medical History by Treatment Group – Safety Population – PSC06

System Organ Class	Flublok n=300 (%)	Fluzone n=302 (%)	Total n=602 (%)
#Subjects with at least one medical history	280 (93)	288 (95)	568 (94)
Allergies	145 (48)	131 (43)	276 (46)
Autoimmune disease	1 (<1)	1 (<1)	2 (<1)
Blood	38 (13)	42 (14)	80 (13)
Cancer	13 (4)	12 (4)	25 (4)
Cardiovascular	122 (41)	134 (44)	256 (43)
Gastrointestinal	70 (23)	79 (26)	149 (25)
Genital/reproductive	128 (43)	143 (47)	271 (45)
HEENT	72 (24)	84 (28)	156 (26)
Immunodeficiency	0	1 (<1)	1 (<1)
Kidney	12 (4)	13 (4)	25 (4)
Liver	2 (<1)	6 (2)	8 (1)
Lungs	45 (15)	51 (17)	96 (16)
Lymph glands	1 (<1)	0	1 (<1)
Metabolic/endocrine	88 (29)	95 (31)	183 (30)
Musculoskeletal	119 (40)	120 (40)	239 (40)
Nervous system	25 (8)	21 (7)	46 (8)
Pancreas	8 (3)	5 (2)	13 (2)
Psychiatric illness	51 (17)	56 (19)	107 (18)
Skin	37 (12)	31 (10)	68 (11)

Source: Table 14.1.6, Module 5, Volume 26, p86. Confirmed by review of the electronic datasets.

Reviewer comment: The proportions of subjects with specific categories of past medical history were very similar between each treatment group.

- Of the two subjects with a history of autoimmune disease, the datasets indicate that Flublok subject #1449 was a 54 year old female with a history of rheumatoid arthritis in 1994 who was maintained on Enbrel (etanercept) 25mg weekly at the time of the study. Subject #1446, Fluzone group, had a history of depression in 2004, but no other details regarding an autoimmune disease and no immunosuppressive therapy were found in the datasets.

Reviewer comment: It is unclear why subject #1449 was allowed to enroll in the study with concomitant use of etanercept. This should be regarded as a protocol violation. Because the study was small and the results alone would not be considered “pivotal” to product approval, we will include this subject in an evaluable population.

- Fluzone subject #0656 had a diagnosis of immunodeficiency. Review of the datasets indicates that he was a 60 year old male with a history of gout in 2000, on fluoxetine for depression, but not on any immunosuppressive agents.
- Of subjects with a diagnosis of cancer, the datasets reveal that the majority involved skin or breast and were remote in onset. None of these subjects were on immunosuppressive or antineoplastic agents at the time of the study.

Concomitant Medications

Subjects who were taking immunosuppressive agents are summarized in Table 25:

Table 25 Concomitant Immunosuppressive Medications – Safety Population – PSC06

Flublok Subject	Flublok Medication	Flublok Dose	Fluzone Subject	Fluzone Medication	Fluzone Dose
1 subject ¹	methotrexate	15mg q wk	#1241	Azathioprine	50mg qd
15 subjects ²	Flunisolide	nasal	7 subjects	Flunisolide	Nasal
2 subjects	Potent topical corticosteroid	Clobetasol 0.05% oint bid	3 subjects	Potent topical Corticosteroid	Clobetasol 0.05% oint qd-bid
4 subjects	Moderate Topical steroid	various	3 subjects	Moderate Topical steroid	Various
0 subjects	Decadron	n/a	#0426	Decadron	One tendon sheath injection
1 subject ³	hydrocortisone	Per rectum	#1853	Hydrocortisone	Topical
1 subject ⁴	etanercept	25mg q wk	0	Etanercept	n/a

Source: Electronic datasets.

qd= daily; bid= twice daily; q wk= weekly

¹ subject ID #1038

² subjects in both treatment groups used nasal flunisolide for allergic rhinitis

³ subject ID#1448

⁴ subject ID#1449

Reviewer comment: Twenty-two Flublok and 15 Fluzone subjects received topical or intranasal corticosteroids during the study. These were allowed by the protocol and would not be expected to have significantly impacted the immunogenicity results. It is possible that the 2 Flublok recipients who received methotrexate and etanercept, respectively, and the one Fluzone recipient who received azathioprine may have been mildly to moderately immunosuppressed from these therapies and may not have responded optimally to the study vaccines. The few subjects who received these therapies, however, were unlikely to have significantly impacted the overall immunogenicity results of the study.

8.1.2.2.2 Immunogenicity Endpoints

Primary Immunogenicity Endpoints

The results of the primary endpoint analyses for the proportion of subjects who achieved a post-vaccination HAI titer of $\geq 1:40$ and for the proportion of Flublok recipients who achieved seroconversion or significant increase in HAI titer (4-fold rise in HAI titer to at least 1:40) at Day 28 are presented in Table 26.

Table 26 Percent Seroconversion or Significant Increase in HAI Titer and Post-vaccination HAI $\geq 1:40$ – Flublok Evaluable Population – PSC06

Strain	% 4-fold rise Flublok n=299	% HAI $\geq 1:40$ Flublok n=299
A/SolomonIslands (H1N1) n(%) 95%CI PASS?*	216 (72.2) (66.8, 77.2) Yes	288 (96) (93.5, 98.1) Yes
A/Wisconsin (H3N2) n(%) 95%CI PASS?	183 (61.2) (55.4, 66.8) Yes	255 (85) (80.8, 89.1) Yes
B/Malaysia n(%) 95%CI PASS?	122 (40.8) (35.2, 46.6) NO	278 (93) (89.5, 95.6) Yes

Source: Table 14.2.1.1, Module 5, Volume 26, pp 87 and 107, CR Vol 2 pp108 and 128.

%HAI $\geq 1:40$ = proportion with postvaccination HAI titer $\geq 1:40$.

*PASS: For %4-fold rise, successful immune response defined by FDA criteria as the lower bound of the 2-sided 95% CI should meet or exceed 40%. For %HAI $\geq 1:40$, successful immune response defined by FDA criteria as the lower bound of the 2-sided 95% CI should meet or exceed 70%.

Results in bold font indicate failure to meet acceptance criteria.

- Flublok exceeded FDA criteria for seroconversion/significant increase in HAI titer for both H1N1 and H3N2 strains but missed this endpoint for the B strain. Flublok exceeded FDA criteria for the proportion of subjects with a Day 28 post-vaccination HAI titer $\geq 1:40$.

Reviewer comment: *Flublok met 5 of the 6 pre-specified immune response primary endpoints for success, but missed the seroconversion endpoint for the B strain. Low immune responses to the B strain in older individuals have been observed following immunization with other TIVs.*

Secondary Immunogenicity Endpoints

The two pre-specified criteria for non-inferiority of Flublok against Fluzone were:

- The UB of the 2-sided 95% CI of the GMT ratio ($\text{GMT}_{\text{US licensed TIV}}/\text{GMT}_{\text{Flublok}}$) 28 days post-vaccination should not exceed 1.5; and
- The UB of the 2-sided 95% CI on the difference between the SCRs ($\text{SCR}_{\text{US licensed TIV}} - \text{SCR}_{\text{Flublok}}$) should not exceed 10%.

Table 27 presents the GMT ratio at Day 28 of Fluzone to Flublok for each vaccine antigen.

Table 27 GMTs and GMT Ratio Fluzone to Flublok at Day 28 – Evaluable Population – PSC06

Visit/ Endpoint	Treatment	H1	H3	B strain
Day 0 GMT	Fluzone n=302	27.77	18.20	49.18
Day 0 GMT	Flublok n=299	28.71	18.57	48.49
Day 28 GMT	Fluzone n=302	139.74	60.88	116.03
Day 28 GMT	Flublok n=299	181.34	105.41	110.93
Day 28 GMT Ratio UB 95%CI	Fluzone/Flublok	0.79	0.62	1.09
PASS non-inferiority?*	Fluzone/Flublok	YES	YES	YES

Source: Table 14.2.2.1, Module 5, Volume 26, p97, CR Vol 3, p. 118

*PASS=successful non-inferiority by FDA Guidance criteria defined as the upper bound (UB) of the 2-sided 95% CI of the GMT ratio ($\text{GMT}_{\text{US licensed TIV}}/\text{GMT}_{\text{Flublok}}$) 28 days post-vaccination should not exceed 1.5

Reviewer comment: *Non-inferiority was demonstrated for all three strains.*

Table 28 presents the difference between seroconversion/significant increase rates between Fluzone and Flublok for each vaccine antigen.

Table 28 Difference in Seroconversion/4-fold rise (SCR) in HAI titers Fluzone to Flublok - Evaluable Population – PSC06

Strain	SCR Flublok (point estimate)	SCR Fluzone (point estimate)	Difference: SCR TIV –SCR Flublok (95% CI)	PASS?*
H1N1	72.2	66.2	-6.0 (-13.4, 1.4)	YES
H3N2	61.2	43.7	-17.5 (-25.4, -9.5)	YES
B strain	40.8	41.1	0.3 (-7.7, 8.2)	YES

Source: Table 14.2.1.1, Module 5, Volume 26, p87, CR Vol 3, p.108.

PASS = successful non-inferiority by FDA Guidance criteria defined as the upper bound (UB) of the 2-sided 95% CI on the difference between the SCRs (SCR US licensed TIV – SCR Flublok) should not exceed 10%.

Reviewer comment: *Flublok was non-inferior to Fluzone by FDA criteria having met the secondary immunogenicity endpoints for each antigen contained in the vaccine. The statistical reviewer also concluded that the study met the non-inferiority endpoints. However, because the SAP did not address multiplicity for the secondary endpoint analyses, these results should be interpreted with some caution.*

Clinical Efficacy Results

Summary data for the subjects in each treatment group who experienced an ILI (reporting a flu symptom card score of 2 or more), including culture results and efficacy estimates, are presented in Table 29.

Table 29 Clinical Efficacy of Flublok against Culture-Confirmed Influenza – PSC06

PSC06 2007-2008	Flublok n=300	Fluzone n=302	--	--
Endpoint characteristic	#cases (%)	#cases (%)	Relative Efficacy ¹	(95% CI)
Matched strains	0	0	n/a	n/a
Regardless of Match-All strains	7 (2.3)	4 (1.3)	-76.2	(-720.7, 55.2)
Regardless of Match-A/H1N1	1 (0.3)	0	-	(-, 97.4)
Regardless of Match-A/H3N2	3 (1.0)	1 (0.3)	-202	(-1575.5, 75.7)
Regardless of Match-B	3 (1.0)	3 (1.0)	-0.7	(-652, 86.5)
CDC-ILI	7 (2.3)	3 (1.0)	-134.9	(-1307.7, 46.4)
Any ILI	7 (2.3)	4 (1.3)	-76.2	(-720.7, 55.2)

Sources: CR Module 5, Vol 3, Tables 14.2.5, p139 and Table 14, p65; Original BLA submission Table 14.2.5, module 5, Vol 10, p222. Amendment 0.17, Response to IR Tables 2 and 4, p5-7 (6-19-09).

¹Relative Protective Efficacy (VE)= (1 – RR) x 100

RR = relative risk = (proportion Flublok positive / proportion Fluzone positive)

Reviewer comment: *None of the influenza isolates obtained from subjects with either CDC-ILI or non-CDC-ILI respiratory illness were antigenically matched to the 2007-2008 vaccine strains. Neither pre-specified secondary efficacy endpoint could, therefore, be evaluated. The low attack rates for all strains regardless of antigenic*

match resulted in wide CIs around post-hoc analyses of relative efficacy and did not allow meaningful conclusions.

Immunogenicity Conclusions PCS06

- Vaccination of healthy adults 50 to 64 years of age with a single dose of trivalent rHA vaccine 135µg elicited an immune response which met 5 of the 6 pre-specified primary immunogenicity endpoints of seroconversion and proportion of subjects with a minimum post-vaccination HAI titer of 1:40 for the three vaccine antigens. Flublok missed the seroconversion endpoint for the B strain.
- Flublok met all 6 pre-specified secondary endpoints for GMT ratios and difference in seroconversion/significant increase rates. Flublok demonstrated non-inferiority to Fluzone by these criteria to all three antigen strains contained in the vaccine. Results of the secondary endpoint analyses should be treated with some caution because the SAP did not address multiplicity.
- The relative efficacy of Flublok to Fluzone could not be evaluated in this study because of the small number of cases of culture-confirmed influenza and antigenic mismatch.

8.1.2.2.3 Safety Outcomes

The Safety Population was comprised of all 602 subjects who received a single injection of Study Vaccine including 300 subjects in the Flublok group and 302 subjects in the Fluzone group.

Deaths and Serious Adverse Events

- No deaths were reported during the study.
- SAEs through EOIS (Day 180) are presented in Table 30. Four SAEs were reported in this study, two in each treatment group. Only one appears to have been related to Flublok.

Table 30 Serious Adverse Events through EOIS (Day 180) – CSR – PSC06

Group	Subject ID (sex/age)	SAE	Onset	Severity	Causality	Tx	Outcome
Flublok	01-0036-(b)(6) (M/57)	Vasovagal Syncope	10min	Mod	Related	ER	Resolved
Flublok	03-0846-(b)(6) (F/53)	Pancreatitis Acute	78d	Mod	Not rel	Hosp	Resolved
Fluzone	03-1089-(b)(6)	Prostate Cancer	161d	Severe	Not rel	Hosp	Resolved, Sequelae
Fluzone	04-1450-(b)(6)	Cerebrovascular Accident	71d	Severe	Not rel	Hosp Med	Resolved, Sequelae

Source: Case narratives, CSR, CR Module 5, Vol. 3, pp78-86, and electronic datasets.

Tx=treatment; Mod=moderate; Not rel=not related; ER=emergency room; Hosp=hospitalized; Med=medications

Reviewer comment: The one related SAE is compatible with the diagnosis of vasovagal syncope due to phlebotomy and/or IM injection. No evidence was reported that would suggest an anaphylactic or hypersensitivity reaction. Vasovagal syncope after phlebotomy and IM injection is not an unexpected event.

Reviewer comment: Case summaries were reviewed for the other three subjects whose SAEs occurred more than 70 days post-vaccination. The reviewer concurs with the investigators that these SAEs were not related to receipt of study vaccines.

Unsolicited Adverse Events According to Severity and Vaccine-Relatedness

Table 31 summarizes the Applicant's report of Unsolicited AEs that occurred from Day 0 to Day 28 and SAEs through the end of the study period (Day 180) according to treatment group, severity, and vaccine-relatedness.

Table 31 Unsolicited AEs (Applicant's Report) – Safety Population – PSC06

Parameter	Grade	Flublok n=300 (%)	Fluzone n=302 (%)	Overall n=602 (%)
Subjects with \geq one AE	All grades	43 (14)	53 (18)	96 (16)
Severity of AEs	Mild	36 (12)	33 (11)	69 (11)
Severity of AEs	Moderate	7 (2)	18 (6)	25 (4)
Severity of AEs	Severe	0	2	2
Serious AEs (SAEs)	All SAEs	2 (<1)	2	4 (<1)
Serious AEs	Deaths	0	0	0
Vaccine relationship	Not related	23 (8)	31 (10)	54 (9)
Vaccine relationship	Possibly related	14 (5)	17 (6)	31 (5)
Vaccine relationship	Related	6 (2)	5 (2)	11 (2)

Source: Tables 14.3.1.5, 14.3.1.9, and 14.3.1.21, Module 5, Volume 26, pp 127, 153 and 200, CR Vol 3, pp 149, 175, and 222, and evaluation of electronic datasets.

- The overall rate of subjects reporting at least one AE was low (16%), and was slightly higher for Fluzone (18%) than for Flublok (14%). Only two treatment-emergent AEs were characterized as severe in this study. No Flublok recipients were reported as experiencing severe Unsolicited AEs. Overall, most subjects who experienced Unsolicited AEs reported events of mild intensity (12% of Flublok and 11% of Fluzone subjects respectively), while 2% of Flublok and 6% of Fluzone subjects reported Unsolicited AEs of moderate intensity. Twenty percent of Flublok recipients and 22% of Fluzone recipients experienced AEs that were considered related or possibly related to the study vaccine.

Events that Occurred in Fewer than 0.5% of Subjects but of Potential Interest:

Although individual AEs were reported at low frequency, the datasets were examined more closely for safety signals, in particular for autoimmune or hypersensitivity phenomena, and for idiosyncratic reactions. Review of electronic datasets for nervous system disorders, musculoskeletal and connective tissue disorders, and skin and subcutaneous tissue disorders revealed only rare, non-severe events balanced between Flublok and Fluzone recipients. Review of electronic datasets for immune system disorders also was unremarkable except for one case of urticaria occurring in one Flublok recipient.

- Urticaria:** Subject #0266 was vaccinated with Flublok on October 23, 2007. On October 27, 2007, four days post-vaccination, the subject was reported to have

experienced hives. The event was assessed as non-serious, mild in intensity and possibly related to the study vaccine. The hives resolved without sequelae after treatment with medication on October 27, 2007.

- **Oculorespiratory Syndrome:** Search of the datasets for the terms “conjunctivitis” and “red eyes” yielded only one Flublok recipient, #0275 who reported conjunctivitis without associated symptoms, 20 days post-vaccination. This event was not suggestive of ORS. No Fluzone recipients reported conjunctivitis during this study.
- **Rash:** The Applicant was asked specifically to provide narratives and CRFs for any subject who experienced severe (Grade 3) rash, hypersensitivity of any intensity/severity grade, or pregnancy. The Applicant replied that no such events occurred in this study.

Unsolicited Adverse Events that Occurred in $\geq 0.5\%$ of Subjects

Table 32 summarizes all Unsolicited AE's that occurred from Day 0 through Day 28 in at least 0.5% of subjects (i.e., in at least 2 subjects) regardless of relationship to the study vaccine. Events are categorized according to MedDRA SOC and PT. Subjects experiencing multiple AEs were counted once per body system and once per PT.

Table 32 Unsolicited Adverse Events by MedDRA SOC and PT the Occurred in $\geq 0.5\%$ of Subjects in either Treatment Group – Safety Population – PSC06

System Organ Class Preferred term	Flublok n=300 (%)	Fluzone n=302 (%)
Subjects with at least one AE	43 (14)	53 (18)
Gastrointestinal disorders	6 (2)	0
Diarrhea	4 (1.3)	0
General disorders and administration site conditions	5 (1.7)	7 (2.3)
Fatigue	0	2 (0.6)
Injection site erythema	5 (1.7)	1 (0.3)
Immune system disorders	1 (0.3)	0
Urticaria	1 (0.3)	0
Infections and infestations	6 (2.0)	16 (5.3)
Nasopharyngitis	1 (0.3)	3 (1.0)
URI*	3 (1.0)	3 (1.0)
Injury, poisoning and procedural complications	2 (0.7)	3 (1.0)
Musculoskeletal and Connective tissue disorders	8 (2.7)	11 (3.6)
Arthralgia	2 (0.7)	1 (0.3)
Back pain	2 (0.7)	4 (1.3)
Nervous system disorders	8 (2.7)	3 (1.0)
Sinus headache	2 (0.7)	1 (0.3)
Respiratory, thoracic, and mediastinal disorders	9 (3.0)	16 (5.3)
Cough	5 (1.7)	2 (0.6)
Nasal congestion	3 (1.0)	3 (1.0)
Pharyngolaryngeal pain	4 (1.3)	9 (3.0)
Rhinorrhea	4 (1.3)	5 (1.6)
Skin and subcutaneous disorders	0	1 (0.3)
Rash	0	1 (0.3)

n=number of subjects

%=percentage of subjects experiencing a specific AE

*URI=upper respiratory infection

Bold font indicates treatment group and SOC category.

Source: Table 14.3.1.1, Module 5, Volume 26, pp118-121, CR Vol 3, pp140-143, and review of the electronic datasets.

Reviewer comment: The frequencies of Unsolicited AEs reported by the Applicant were low and were similar between the two treatment groups. Evaluation of the electronic datasets confirmed that the numbers of subjects experiencing AEs in each PT and SOC category were identical to the Applicant's report.

- Of all Unsolicited AEs, those most frequently considered vaccine-related in the Flublok group were: injection site erythema (2%); cough (1%); diarrhea (1%); pharyngolaryngeal pain (1%); rhinorrhea (1%); and nasal congestion (0.7%). There were relatively more cases of injection site erythema (5 to 1), diarrhea (3 to 0), and cough (4 to 0) among Flublok subjects relative to Fluzone recipients. Most cases of vaccine related or possibly related AEs were mild and resolved without sequelae by Day 28.

Reviewer comment: Assessment of attribution of Unsolicited AEs experienced by recipients of Flublok as compared to Fluzone did not reveal unusual patterns or raise safety concerns.

8-Day Solicited Reactogenicity Events (Day 0-Day7)

Table 33 presents Solicited AEs (reactogenicity) by treatment group and severity. Data is shown only for all events (mild, moderate or severe) and severe events within each category. The table also compares the Applicant's paper submission report with data derived from the reviewer's evaluation of the electronic datasets.

Table 33 Solicited Local and Systemic Reactogenicity Events within 8 Days of Vaccination, Flublok vs. Fluzone, According to Severity – Safety Population – PSC06

Solicited AE	Severity Grade *	Flublok Dataset n=300	Flublok Applicant n=300	Fluzone Dataset n=302	Fluzone Applicant N=302
Solicited AE	Severity grade	n (%)	n (%)	n (%)	n (%)
Fever	Any grade 1,2,3	3 (1.0)	3 (1)	1 (0.3)	1 (<1)
Fever	Severe	0	0	0	0
Injection site pain	Any grade 1, 2, 3	154 (51.3)	154 (51.3)	165 (55)	165 (55)
Injection site pain	Severe (3)	1 (0.3)	1 (<1)	0	0
Injection site bruising	Any grade 1, 2, 3	16 (5.3)	16 (5.3)	14 (5)	14 (5)
Injection site bruising	Severe	0	0	0	0
Measured redness	Any grade 1, 2, 3	24 (8.0)	24 (8.0)	25 (8.3)	25 (8.3)
Measured redness	Severe	5	5 (2)	3	3 (<1)
Measured swelling	Any grade 1, 2, 3	25 (8.3)	25 (8.3)	30 (9.9)	30 (9.9)
Measured swelling	Severe	2	2 (<1)	4	4 (1)
Fatigue	Any grade 1, 2, 3	40 (13.3)	40 (13.3)	62 (20.5)	62 (20.5)
Fatigue	Severe	2	2 (<1)	3	3 (<1)
Shivering, chills	Any grade 1, 2, 3	12 (4.0)	12 (4.0)	15 (5.0)	15 (5.0)

Solicited AE	Severity Grade *	Flublok Dataset n=300	Flublok Applicant n=300	Fluzone Dataset n=302	Fluzone Applicant N=302
Solicited AE	Severity grade	n (%)	n (%)	n (%)	n (%)
Shivering, chills	Severe	0	0	0	0
Joint pain	Any grade 1, 2, 3	15 (5.0)	15 (5.0)	19 (6.3)	19 (6.3)
Joint pain	Severe	1	1 (<1)	1	1 (<1)
Muscle pain	Any grade 1, 2, 3	40 (13.3)	40 (13.3)	41 (13.6)	41 (13.6)
Muscle pain	Severe	0	0	1	1 (<1)
Headache	Any grade 1, 2, 3	59 (19.7)	59 (19.7)	63 (20.9)	63 (20.9)
Headache	Severe	0	0	1	1 (<1)
Nausea	Any grade 1, 2, 3	13 (4.3)	13 (4.3)	15 (5.0)	15 (5.0)
Nausea	Severe	0	0	1	1 (<1)

n = number of subjects in treatment group

Applicant states that subjects with multiple symptoms in the same category were counted once per category using the symptom with the maximum grade.

Source: Applicant's Tables 14.3.6.2 and 14.3.6.5, Module 5, Volume 26, pp204-206 and 213, CR Vol 3, pp226-228 and 235.

*Grading system for reactogenicity events

Grade	Injection site (mm)	Fever	Symptoms
0 (none)	<10mm	<100.4°F	None
1 (mild)	≥10mm and < 20mm	≥100.4 to 101.1°F	Noticed it, but it didn't interfere with usual activities at all
2 (moderate)	≥20mm and <50mm	≥101.1 to 102.1°F	Had it, and it was bad enough to prevent a significant part of usual activities
3 (severe)	≥50mm.	≥102.2°F	Had it, and it prevented most or all of normal activities, or had to see a doctor for prescription medicine

- Overall, the majority of reactogenicity events in both treatment groups were reported as mild and very few were reported as severe.
- The most common reactogenicity events among Flublok recipients were injection site pain (51.3%), headache (19.7%), myalgia (13.3%), and fatigue (13.3%). Similar rates were reported among the Fluzone recipients: injection site pain (55%), headache (20.9%), myalgia (13.6%), with the exception of a higher rate of fatigue (20.5%).

Reviewer comment: The datasets were also evaluated for the occurrence of fever. Five hundred ninety-three subjects recorded their temperature in the diary card on 4705 occasions between Day 0 and Day 7. Of these, all 4705 temperature recordings appeared to be associated with the symptom of fatigue or lack of energy. No temperature appeared to be recorded concomitantly with other symptoms such as shivering or chills. Of the 4705 recorded temperatures, only four were above 100.4° F and are presented in Table 34.

Table 34 Fever $\geq 100.4^{\circ}\text{F}$ Day 0 to Day 7 – Electronic Datasets Safety Population – PSC06

Patient ID	Group	Day	Temperature °F
0258	Flublok	2	100.4
0275	Flublok	1	100.6
0656	TIV	3	100.4
2058	Flublok	4	100.4

- Similar to the results from PSC04, the occurrence of pyrexia was low overall, but there were more cases of mild pyrexia in the Flublok group (n=3, 1.0%) than in the Fluzone group (n=1, 0.3%).
- The rates of other local injection site reactions, chills, arthralgias, and nausea were less than 10% and very similar between the two treatment groups.

Pregnancies

There were no pregnancies reported in either treatment group from Day 0 through the end of the study period.

Discontinuations Due to Adverse Events

No subjects were discontinued from the study due to an adverse event. As noted in the SAE section, Fluzone subject 03-1089 withdrew because of a diagnosis of prostate cancer after participation in the study was completed.

Case Report Forms Reviewed for Study PSC06

- SAE Vasovagal Syncope: Subject #0036, initials b(6), site 01. Please see the discussion in the “Deaths and SAE’s” section.
- The CRFs for subjects 03-0846, 03-1089, and 04-1450 were also reviewed for assessment in the “Deaths and Serious Adverse Events” section of this review.

Vital Signs

There were no unexpected treatment-emergent trends or patterns in vital signs identified following Flublok administration in study PSC06.

Laboratory Evaluation

There were no routine clinical laboratories performed for the study other than screening urine pregnancy tests.

8.1.2.3 Comments Study PSC06: Safety Conclusions

- No deaths occurred in either treatment group as of the time of the database lock, and no subjects were discontinued due to an adverse event. Four SAEs were reported over the 6 month post-vaccination period. Vasovagal syncope occurred in a Flublok recipient and was the only SAE considered to be vaccine-related.
- The most common reactogenicity events following vaccination with either Flublok or Fluzone were injection site pain, headache, myalgia, and fatigue. Overall, reactogenicity events were mild and the frequencies very similar between the two groups with the exception of pyrexia, which was reported in the datasets more often in the Flublok group (1% versus 0.3%), and fatigue which was

reported less often in the Flublok group. Reactogenicity events to Flublok were expected and occurred with frequencies similar to licensed TIVs.

- The overall rate of Flublok recipients reporting at least one Unsolicited AE in the 28 days post-vaccination was low, 14%, and was comparable to the rate reported for Fluzone (18%). Most events were mild, none were considered severe, and rates were similar between treatment groups.
- A single episode of mild urticaria occurred in a subject four days after receiving Flublok and was considered possibly related to Flublok. No other cases of hypersensitivity were reported. Hypersensitivity events will be monitored in future trials and as part of the post-marketing pharmacovigilance plan.

8.1.2.4 Comments Study PSC06: Safety and Efficacy Conclusions

- In adults 50 to 64 years of age, vaccination with a single dose of 135mcg was immunogenic and exceeded 5 of the 6 co-primary endpoints for seroconversion and for the proportion with post-vaccination titer $\geq 1:40$. The B strain failed to meet one of the two co-primary endpoints. In addition, Flublok met all 6 of the secondary immunogenicity endpoints required by FDA criteria to demonstrate non-inferiority to a US-licensed TIV. Overall, the safety and immunogenicity data appear to have integrity and support licensure, despite some statistical limitations related to multiplicity. However, concerns over the HAI assay and the impact of these concerns on interpretation of the immunogenicity results persist. Please see Sections 9 and 12 for further discussion of the immunogenicity results in adults 50 years and older.
- The relative clinical efficacy of Flublok to Fluzone could not be evaluated in this study because of the small number of cases of culture-confirmed influenza and because of antigenic mismatch. Thus, study PSC06 is not able to support full (“traditional”) approval of Flublok in this age group based on clinical efficacy endpoints.
- No unusual trends, patterns or safety signals were noted in the review of six months of safety data.

8.1.3 Trial #3

8.1.3.1 Applicant’s Protocol Number PSC03 (BB-IND 11951) “Comparison of the Immunogenicity, Safety and Reactogenicity of Flublok, Trivalent Recombinant Baculovirus-Expressed Hemagglutinin Influenza Vaccine, to a Licensed Egg-Grown Influenza Vaccine (Fluzone) in Ambulatory Elderly Adults.”

8.1.3.1.1. Objective/Rationale:

Primary Objective:

- To compare the immunogenicity of Flublok and a licensed egg-grown TIV in ambulatory elderly adults (65 years or older).

Secondary Objectives:

- To compare the safety and reactogenicity of TIV and Flublok.

- To compare the relative efficacy of the two vaccines for prevention of culture-positive CDC-ILI and/or culture-positive medically attended acute respiratory illness during the 2006-2007 influenza epidemic season.

8.1.3.1.2 Design Overview

- PSC03 was a Phase 3, prospective, randomized, modified double-blind, active-controlled, multi-center clinical trial to compare the immunogenicity, safety, and reactogenicity of Flublok versus TIV in ambulatory, medically stable adults age 65 and older. The licensed TIV used in this study was Fluzone manufactured by sanofi-pasteur.
- A total of 870 subjects at 6 study sites were stratified by previous vaccination status (2005-2006) and then randomized in a 1:1 ratio to receive one dose of Flublok or TIV.
- Subjects participated until the EOIS visit (up to 9 months post-vaccination for individual subjects), and reported to the clinic for a minimum of three regular visits. Subjects who experienced ILI symptoms called the clinic and, if warranted, reported to the clinic for an illness visit. All subjects with (1) signs and symptoms of illness consistent with CDC-ILI, and/or (2) had sought medical care for their acute respiratory illness, had nasal and throat swabs (NS/TS) collected at the study site for viral culture.
- Study Period
 - First subject enrolled: October 9, 2006.
 - Last subject completed: July 9, 2007.

8.1.3.1.3 Population

- 870 healthy, medically stable adult male and females ≥ 65 years of age who met the inclusion/exclusion criteria.
- Exclusion criteria similar to PS04 and PSC06 including history of Guillain Barre Syndrome (GBS).

8.1.3.1.4 Products Mandated by the Protocol

Flublok was administered once as a 0.5mL dose IM in the non-dominant deltoid muscle. Each dose contained a total of 135 μ g recombinant hemagglutinin as determined by SRID, representing the HA derived from the three WHO recommended strains of influenza virus for the 2006-2007 Northern Hemisphere influenza season:

- 45 μ g A/New Caledonia/20/99 (H1N1)
- 45 μ g A/Wisconsin/67/05 (H3N2)
- 45 μ g B/Ohio/01/05 (B strain)

Flublok Lot number: 50-06019

Fluzone, sanofi Pasteur, 2006/2007 formulation, was the TIV comparator. Each 0.5ml dose contained a total of 45 μ g HA:

- 15 μ g A/New Caledonia/20/99 (H1N1)
- 15 μ g A/Wisconsin/67/2005 (H3N2)
- 15 μ g B/Malaysia/2506/2004 (B strain)

Reviewer comment: Flublok and Fluzone differed with respect to the selection of the B strain antigens. However, these were considered antigenically related by the WHO reference laboratories and interchangeable for purposes of vaccine production and inclusion in the 2006-2007 formulation.

Fluzone was provided in multi-dose vials and was injected as a 0.5mL dose IM in the non-dominant deltoid muscle of the arm. Two lots of Fluzone were used in the study: U2177AA and U2199AA.

8.1.3.1.5 Endpoints

Safety Endpoints

- Frequencies of AEs and SAEs solicited in clinic, via memory aids and telephone and/or clinic follow-up, and targeted physical exam.

Primary Immunogenicity Endpoints

- Proportion of subjects in each vaccine group who seroconverted defined as: (1) a ≥ 4 -fold rise in HAI antibody in subjects who were seropositive at baseline; or (2) the attainment of a titer of $\geq 1:40$ in subjects who were seronegative at baseline (HAI titer $< 1:10$) against each of the three antigens contained in the vaccine, 28 days after vaccination.
- GMTs of serum HAI antibody against each of the three antigens contained in the vaccine 28 days after vaccination.

Secondary Immunogenicity/Efficacy Endpoints

- Proportion of subjects in each vaccine group achieving a post-vaccination HAI antibody titer (Day 28) of $\geq 1:40$ or greater to each vaccine antigen.
- GMTs, SCRs, and proportions of subjects in each vaccine group with serum HAI antibody titers of $\geq 1:40$ at the EOIS visit.
- Proportion of subjects in each vaccine group who experience culture-positive CDC-ILI and/or culture-positive medically attended acute respiratory illness during the 2006-2007 influenza season.

Exploratory immunogenicity endpoints

- The following parameters were calculated for each of the following subgroups: (1) subjects ≥ 75 years of age; (2) subjects who received a licensed influenza vaccine (TIV) the previous year (i.e., 2005-2006 influenza season); and (3) subjects with baseline HAI antibody titers of $< 1:40$:
 - Number and proportion of subjects exhibiting a titer of $\geq 1:40$ on Day 28 and at EOIS;
 - Ratio of GMTs (GMT TIV/GMT Flublok) on Day 28 and at EOIS;
 - SCRs at Day 28 and EOIS (as defined by the proportion of subjects with a ≥ 4 -fold rise in HAI titer response from baseline to EOIS).

Reviewer comment: Data from these exploratory analyses will not be presented or discussed in this review except briefly in Section 9, Overview of Efficacy.

Validation of the HAI assay – Please see Section 4.4 and PSC04 Section 8.1.1.1.5

Adverse events (AEs) were defined as any event, side effect, or other untoward medical occurrence, including dosing errors that may be present during treatment with a pharmaceutical product and may or may not be related to treatment. AEs were to be followed until resolution.

Solicited Adverse Events (Reactogenicity): Frequencies of local and systemic reactions for 8 days following vaccination (Day 0 through Day 7), noted on the subject Memory Aid and assessed on the Day 8 contact.

- Local (injection site) reactions: included local pain; bruising; redness, soft swelling; and hard swelling (induration). The grading scale for measured injection site reactions (redness, induration) was the same as for PSC04 and PSC06.
- Systemic reactions: included fever ($\geq 100.4^{\circ}\text{F}$); fatigue; tiredness/lack of energy; shivering (chills); joint pain; muscle pain; headache; nausea; and sweating.

Reviewer comment: The original protocol planned to assess fever, chills, fatigue/malaise, myalgia, joint ache, headache and nausea. These variables are identical to PSC06 and PSC04. The final study report has additional categories of tiredness/lack of energy (which appears redundant or similar to fatigue) and sweating. The differences in the variables themselves appear minor, but the lack of uniformity between studies made direct comparison slightly more difficult.

- The functional scale used by subjects for self-assessment of systemic reactogenicity was the same as the one used in PS04.
- Grading scale for fever:
 - Grade 1 (mild): $\geq 99.6^{\circ}$ to $< 100.4^{\circ}\text{F}$
 - Grade 2 (moderate): ≥ 100.4 to $< 102^{\circ}\text{F}$
 - Grade 3 (severe): $\geq 102^{\circ}\text{F}$

Reviewer comment: The functional scale for grading systemic reactions was identical to that used in study PSC04 and PSC06. However, mild fever was defined as $\geq 99.6^{\circ}$ to $< 100.4^{\circ}\text{F}$ in this study, but as $\geq 100.4^{\circ}\text{F}$ to 101.1°F in PSC04 and PSC06. This is a relatively small difference and, in the reviewer's opinion, should not cause a significant difference in the overall results.

Unsolicited (treatment-emergent) AEs: collected from Day 0 through Day 28.

- Severity grade was based on NCI Common Toxicity Criteria (CTCV3) used in PS04 and PS06
- AEs were assessed as not related, related or unknown relatedness to the study vaccine

Reviewer comment: This classification system differs from that used in PSC04 and PSC06 (not related, related, and possibly related). For purposes of the review, any event that could not be assessed as not related to the study vaccine was considered related or, in the case of unknown relationship, possibly related.

Serious Adverse Events: collected from Day 0 to the EOIS visit (up to 9 months).

8.1.3.1.6 Surveillance Monitoring

- Please see Schedule of Procedures and Design Overview Section 8.1.4.1.2.
- All subjects were observed for at least 15 minutes immediately following vaccination and were contacted by telephone on Day 8 by study personnel to solicit reactogenicity symptoms for Day 0 to Day 7 of the Memory Aid.
- At the Day 28 visit subjects had a medical history review and a targeted physical exam if indicated. Changes in health status, concomitant medications, and AEs were reviewed and recorded. HAI titers were drawn.
- Follow-up Phone Calls/Flu Surveillance
 - Active surveillance for influenza was to begin when 2 or more cases were positive for influenza in community surveillance or laboratory reports. Surveillance was to end after three consecutive weeks without a positive sample from either community surveillance or from study subjects, unless reports from national (CDC) surveillance showed continued circulation of influenza due to a strain that had not already occurred at that study site. This time point was defined as the EOIS.

Reviewer comment: Definition of the active surveillance period is different from PSC04 and PSC06 which is based on the percentage of positive samples.

- During this flu-surveillance period, subjects were to receive phone calls from study personnel every other week to elicit information regarding the presence or absence of respiratory illness symptoms. If subjects had recorded an influenza symptom score of 2 or greater on the Flu Symptoms Card, they were instructed to contact the clinic to arrange an illness evaluation.
 - Flu symptom scoring for ILI was the same as for PSC04 and PSC06 (Section 8.1.1.1.6).
- Illness Evaluations
 - Subjects were instructed to record respiratory symptoms on weekly Flu Symptoms Cards beginning on Day 0. Subjects with a flu symptoms score of 2 or greater were to contact study personnel and return to clinic for interval medical history and physical exam.
 - NS/TS for viral culture was obtained if the subject met the definition of CDC-ILI and/or if the subject had sought medical care at another institution.
- End of Study Evaluation/End of Influenza Season
 - At the EOIS a final visit was to be made to review medical history, perform exam if indicated, record SAEs or new onset of chronic medical conditions, any other change in health status, and review concomitant medications.
 - SAEs were to be followed until resolution or stabilization.

Reviewer comment: Sample Reactogenicity Memory Aid, Flu Symptoms Card, Case Report Form, Day 8 Telephone Assessment Card, and End of Study Record Card were reviewed and appeared appropriate.

8.1.3.1.7 Statistical Considerations

- Please see the statistical review.
- Randomization and Blinding
 - Subjects were stratified prior to randomization based on whether they received TIV in the 2005-2006 influenza season. They were then randomized to treatment group using a block method with a block size of 6.
 - Investigators, study staff, the Applicant and subjects were blinded to treatment assignment. Each study site designated one staff member who was unblinded to the randomization code, prepared the study vaccines, maintained the treatment log, and administered the vaccine. This unblinded staff member was not allowed to perform any clinical safety or efficacy assessments.
 - A centralized laboratory conducted all testing. Laboratory personnel were blinded to the source and group assignment of the specimens.
- Analysis Populations
 - Safety Population: all randomized subjects who received any dose of study medication were included in all safety analyses.
 - Evaluable Population for Immunogenicity: all randomized subjects who received the correct dose of vaccine and had titers taken at baseline and at Day 28 were included in the immunogenicity analyses at Day 28. Those who had titers measured at baseline, Day 28 and at EOIS were used to assess serological status at EOIS.
 - Evaluable Population for Relative Risk (Relative Efficacy): All subjects who received the correct dose of vaccine.
- Primary Immunogenicity Analysis
 - $H_0: (SCR_{Fluzone} - SCR_{Flublok}) \geq 0.1$
 - $H_a: (SCR_{Fluzone} - SCR_{Flublok}) < 0.1$
 - SCRs were defined as the percentages of subjects with a ≥ 4 -fold increase in HAI antibody titer at Day 28 relative to baseline with a minimum Day 28 titer of 1:40. To meet FDA criteria for non-inferiority, the UB of the two-sided 95% CI on the difference between the SCRs ($SCR_{TIV} - SCR_{Flublok}$) should not exceed 10%. Differences between treatment groups were evaluated using the Chi-Square test.
 - $H_0: (GMT_{Fluzone}/GMT_{Flublok}) \geq 1.5$
 - $H_a: (GMT_{Fluzone}/GMT_{Flublok}) < 1.5$
 - GMTs were calculated for each antigen contained in the vaccine. In order to meet FDA criteria for non-inferiority, the UB of the two-sided 95% CI on the ratio of the GMTs ($GMT_{TIV}/GMT_{Flublok}$) should not exceed 1.5.

- SCRs in each vaccine group, for each strain contained in the vaccine were calculated, along with 2-sided 95% CIs, to determine whether the LB of the 2-sided 95% CI met FDA criteria of $\geq 30\%$
- Secondary Immunogenicity Analysis
 - The number and proportion of subjects with an HAI titer of $\geq 1:40$ on Day 28 and at EOIS were summarized by treatment group and overall, along with 95% CIs. The LB of the 2-sided 95% CI should meet or exceed 60%.
 - GMT ratio at EOIS was calculated by treatment group and overall, along with 95% CIs.
 - SCR at EOIS was calculated by treatment group and overall, along with 95% CIs.
- Primary Efficacy Outcome
 - Frequency counts and percentages of subjects who experienced a CDC-ILI, positive NS/TS culture for influenza, or both were summarized by treatment group and overall.
 - Relative Risk ($RR = 100 \times \text{relative risk of subjects having a positive culture} = 100 \times PF/PT$, where PF = proportion of subjects receiving Flublok that had a culture-positive CDC-ILI and PT = proportion of subjects receiving TIV that had culture-positive CDC-ILI. The RR for culture-positive CDC-ILI was calculated with 95% CIs for Flublok versus TIV in order to assess relative efficacy.
- Secondary Efficacy Outcome
 - RR for a positive influenza culture was calculated for Flublok versus TIV in order to assess relative efficacy.

Reviewer comment: The study was designed and powered only to test formal null hypotheses for the 2 non-inferiority immunogenicity endpoints, but not clinical efficacy endpoints.

- Summary statistics were used to analyze safety data, demographic data and baseline characteristics.
- Determination of Sample Size: To demonstrate non-inferiority for 2 co-primary endpoints for each of the 3 vaccine antigens, i.e., for 6 co-primary endpoints, 6 comparisons were constructed at a 2-sided α level of 0.05 for an overall power of 80%. The minimum sample size required to ensure 80% power for the test of non-inferiority of Flublok to TIV was calculated as 655 subjects per arm. The trial ultimately enrolled 870 subjects who were randomized to the two arms of the study. (See below).

Reviewer comment: The overall power of the study was presumed to be less than 80% because the study failed to enroll the target sample size of 655 subjects per arm needed to ensure a power of 80% according to the Applicant's calculations. Despite underenrollment, the statistical reviewer felt that the power was adequate to demonstrate that the B strain missed the non-inferiority endpoint because it missed by such a large margin. For further discussion regarding the power of the study, please see the statistical review.

- Subjects who withdrew or who were terminated were not replaced.
- Missing data were not imputed.
- Changes in the Conduct of the Study or Planned Analyses
 - Planned sample size was 1,350 subjects, 675 per arm. However, recruitment was slow, and to ensure that all subjects would be vaccinated in time for the influenza season, enrollment was halted after 870 subjects.
 - Subgroup analyses not included in the pre-specified SAP were subjects ≥ 75 years of age, subjects with prevaccination HAI titers of $< 1:40$, subjects who did and did not receive a licensed TIV in 2005-2006, and subjects according to study site. These endpoints were considered exploratory.
 - The Applicant states that they became aware of several GCP violations at Site 5, Passport Health, Baltimore, MD, during a routine monitoring visit by the CRO. Violations included access by blinded study personnel to the randomization code and improper disposal of study vaccine after administration. It was not clear from the CSR how many staff had access, for how long this occurred, or how many subjects were involved, but the Applicant indicated that these GCP violations pertained primarily to the potential for unblinding nursing personnel who were involved either directly or peripherally in vaccination of subjects and telephone follow-up. Such violations could potentially have biased the safety assessments, but should not have affected HAI results because all laboratory personnel who performed these assays remained blinded. To assess the impact of this break in the blind at Site 5, the Applicant performed the primary and secondary endpoint analyses on Site 5 (n=127) versus the remaining sites (n=743). (Separate analyses for Site 5 located in Section 16.1.13, Module 5, Volume 11, pp667-679). For results of the Applicant's analyses on Site 5, please see Section 8.1.3.2, Results.

Reviewer Comment: The Applicant did not provide information on the number of subjects involved in the potential unblinding at site 5, and subjects at site 5 are included in the review of the Applicant's analyses below. An evaluation of immune responses would not likely be affected by inadvertent unblinding of subjects and the Applicant performed a post-hoc immune response analysis among subjects enrolled at site 5 (See Results section 8.1.3.2). Safety data, however, could be affected by unblinding. This protocol violation was part of the August 29, 2008 CR letter to the Applicant.

Applicant's Complete Response – April 7, 2009 – Item 22: Unblinding at Site Five

- The Applicant was asked to provide additional information regarding the nature of the inappropriate access to the randomization code, the number of subjects affected by this event, treatment assignment of affected subjects, and whether the staff involved also evaluated safety parameters.
- In the CR, the Applicant indicated that, on November 20-22, 2006, the CRO discovered that the blind had not been maintained for 127 subjects enrolled to

date at Site 5. Enrollment was halted pending the results of an investigation. Two study coordinators that were performing blinded screening and randomization were also administering study vaccine (unblinded). This deviation applied to all 127 subjects at Site 5. In addition, the CRO discovered that the used vials of study vaccine had not been saved for an unblinded designee to conduct drug accountability in order to ensure that the assigned drug had been given according to the randomization code.

- The CRO evaluated the site personnel who were responsible for safety monitoring and concluded that AEs were captured appropriately, that no SAEs had been discovered, and that the break in the blind had not compromised subject safety or assessments.
- The PI's response to the CRO's audit was that the blind had not been broken because the study coordinators could not remember the study drug assignment from one day to the next.
- Additional violations discovered by the CRO audit included:
 - Study drug was transported to alternate sites without temperature control or monitoring in place.
 - The Principal Investigator was not consistently assessing causality of AEs per protocol.
- The Applicant indicated that the findings of the CRO audit were initially provided to FDA by telecommunication on December 22, 2006, and were then submitted to BB-IND 11951 Amendment #30, January 25, 2007. The Applicant proposed that they conduct safety and immunogenicity analyses for Site 5 and compare these results with an analysis of the remaining study sites. If no significant difference was found, then data from Site 5 would be included in the datasets for the final analyses. The study was allowed to proceed according to this plan.

Reviewer comment: The Applicant's report suggests that the unblinding of the two study coordinators (who performed eligibility assessments, had access to the randomization code, and administered study vaccine) did not bias the site personnel responsible for safety assessments. The safety and immunogenicity sensitivity analyses also suggest that the breaking of the blind for these 127 subjects did not affect the overall results of the study. The statistical reviewer concluded that the sensitivity analyses demonstrated that results from Site 5 were similar to the other study sites and that results from Site 5 could be pooled with other sites' data. The Reviewer concurs with the statistical reviewer's conclusion that it is reasonable to include this site in the final analyses for study PSC03. For further information, please see the statistical review.

8.1.3.2 Results Study PSC03

8.1.3.2.1 Populations Enrolled and Analyzed

Subject Disposition and Protocol Deviations

Subject disposition and protocol deviations from study PSC03 are presented in Table 35.

Table 35 Disposition of Subjects – PSC03

Disposition	Flublok n=436 (%)	Fluzone N=434 (%)
Randomized	436 (100)	434 (100)
Vaccinated	436 (100)	433 (100)
Completed	428 (98)	426 (98)
Discontinued – All	8 (2)	8 (2)
Discontinued - Due to AE	0	1 (<1)
Discontinued - Lost to follow up	0	1 (<1)
Discontinued - Withdrew consent	1 (<1)	2 (<1)
Discontinued - Died	2 (<1)	2 (<1)
Discontinued - Randomized, not vaccinated	0	1 (<1)
Discontinued - Other	5 (1)	1 (<1)
-overseas travel	1 (<1)	0
-moved	3 (<1)	1 (<1)
-protocol violation	1 (<1)	0
Protocol Deviations - All	7 (1.6)	8 (1.8)
Deviation - Randomized not Vaccinated	0	1 (<1)
Deviation -Visit outside of window	2 (<1)	4 (1)
Deviation - Missing baseline or Day 28 serology data	5 (1)	3 (<1)
Safety Population	436	433
Efficacy Population	431	430
-Previously vax	359	363
-No previous vax	72	67

Source: Table 4 and Figure 1, Module 5, Volume 10, pp47-48; data were confirmed by evaluation of the datasets.

- Of the 16 subjects that did not complete the study, 4 died (2 in each treatment arm) from unrelated causes and one (Fluzone arm) was discontinued due to an AE.
- Regarding Site 5, 127 subjects were enrolled and vaccinated. One was lost to follow-up and did not complete the study.
- As indicated in Section 8.1.4.1.7, Statistical Considerations, GCP violations were found at Site 5 including breaking the blind and improper disposal of study vaccine after administration. Because the Applicant found no significant differences between Site 5 and the other study sites when they compared immunogenicity and safety data, the data from this site was included in the final analyses.

Reviewer comment: The Applicant did not include the subjects involved in the breaking of the blind or those affected by other deviations from GCP at Site 5 (n=127) under Protocol Deviations. The Applicant performed a post-hoc analysis of subjects enrolled at site 5 (see below in immune response results section). Please see CR comments in the previous section “Changes in the Conduct of the Study or Planned Analyses”.

- In addition to the deviations at Site 5, there were 15 other protocol deviations.

Reviewer comment: *These deviations were reviewed, found to be minor, and did not raise concerns regarding the overall acceptability of the data.*

Demographics and Baseline Characteristics

Demographics and baseline characteristics for participants in Study PSC03 are summarized in Table 36.

Table 36 Demographics and Baseline Characteristics – PSC03

Parameter	Category	Flublok N=436 (%)	Fluzone n=433 (%)	U.S. Population July 2007
Race/ethnicity	White/Caucasian	432 (99)	420 (97)	81.3%
Race/ethnicity	Black/ African/American	2 (<1)	7 (2)	13.0%
Race/ethnicity	Latino/Hispanic*	1 (<1)	0	7.4%
Race/ethnicity	Asian	0	2	4.5%
Race/ethnicity	American Indian/ Alaska Native	0	3	1.0%
Race/ethnicity	Native Hawaiian/ Pacific Islander	0	0	0.2%
Race/ethnicity	Other	1 (<1)	1 (<1)	--
Gender	Male	208 (48)	199 (46)	--
Gender	Female	228 (52)	234 (54)	--
Age (years)	Mean (SD)	72.9 (6.66)	73.0 (6.13)	--
Age (years)	Median	71.0	72.0	--
Age (years)	Min-Max	65-92	65-91	--

*Hispanic origin is considered an ethnicity, not a race, and Hispanics may be of any race.

Source: Table 14.1.3, Module 5, Volume 10, p.156; confirmed by evaluation of the datasets.

- The two treatment groups were similar in demographics. The majority of subjects were white (97-99%) and slightly more were female (52-54%). The mean age was 73 years, range 65-92.

Reviewer comment: *The study population was comprised primarily of Caucasian subjects, and there was under representation of African-Americans, Hispanics, and Asians relative to the general U.S. population. Evaluation of the datasets confirmed the Applicant's report.*

Influenza History

The proportion of subjects in each treatment group who reported having received influenza vaccination in the 2005-2006 season is presented in Table 37.

Table 37 Influenza History by Treatment Group PSC03 – Evaluable Population

Influenza Vaccination Status 2005/2006	Flublok n=431 (%)	Fluzone n=430 (%)
Yes	359 (83.3)	363 (84.4)
No	72 (16.7)	67 (15.6)
Total	431	430

Source: review of electronic datasets

Reviewer comment: *The proportion of subjects who received influenza vaccination in the season preceding the study was almost identical in both treatment groups, with approximately 84% of subjects reporting vaccination in 2005/2006.*

Past Medical History

Table 38 presents subjects' past medical history according to treatment group.

Table 38 Past Medical History by Treatment Group - Safety Population – PSC03

System Organ Class	Flublok N=436 (%)	Fluzone N=333 (%)	Total N=869 (%)
# Subjects with at least one medical history	n	n	n
Allergies	176	177	353
Autoimmune disease	1	4	5
Blood	110	119	229
Cancer	84	78	162
Cardiovascular	305	297	602
Gastrointestinal tract	148	146	294
Genital/reproductive	110	126	236
HEENT	155	166	321
Immunodeficiency	0	1	1
Kidney	37	37	74
Liver	16	13	29
Lungs	46	38	84
Lymph glands	4	6	10
Metabolic/endocrine	138	134	272
Musculoskeletal	256	238	494
Nervous system	60	66	126
Pancreas	6	13	19
Psychiatric illness	46	55	106
Skin	63	60	123

Source: review of electronic datasets

- Autoimmune disease was reported by 1 Flublok and 4 Fluzone recipients. Patient 0006 (Flublok) had drug induced lupus that had resolved. Fluzone subjects: #0083 had isolated Raynaud's in 1996; #0535 had polymyalgia and temporal arteritis in 2001; #1105 had scleroderma diagnosed in 1993; and #1199 had chronic fatigue syndrome in 1986.
- Blood: most of these were hyperlipidemias.
- Cancer: most of these were remote and/or cutaneous according to the datasets.
- Immunodeficiency: one subject, #1219 in the Fluzone group, had a PMH of immunodeficiency further described as anxiety in 2002 and insomnia in 2002.

- Pancreas: most of these were diabetics, 3 Flublok and 12 Fluzone subjects with diabetes mellitus type II.
- Lymph glands: one subject (Flublok) had Non-Hodgkins Lymphoma (NHL) in 1997.

Reviewer comment: *Overall, past medical history was similar in the two treatment groups except that there were relatively more Fluzone recipients (n=12) than Flublok recipients (n=3) with diabetes. The datasets describe most of these diabetics as type II and well-controlled or controlled. Review of the concomitant medication datasets for the 5 subjects with history of autoimmune disease revealed that none were taking immunosuppressive medication during the study. The autoimmune illnesses and cancers appeared to be inactive or stable, and to fall within the inclusion/exclusion criteria. An exception was the Flublok subject with NHL who should have been excluded because the eligibility criteria excluded all persons with any history of lymphoproliferative disorders. This subject was diagnosed 10 years prior to the study and was not receiving chemotherapy or steroids during the study. Overall, these baseline medical illnesses appear to have been remote/resolved or chronic and stable. They were mostly similar between treatment groups and would not have been expected to have an impact on the study results.*

Concomitant Medications

The datasets were reviewed for subjects who were taking immunosuppressive medications.

- Antineoplastic agents: one subject, #1112 Flublok group, was using 1% topical bexarotene (Targretin) once a week for cutaneous T-cell lymphoma.
- Systemic corticosteroids: 7 subjects, 5 Flublok and 2 Fluzone recipients, received systemic corticosteroids during the study. Three of these were intra-articular or bursa injections on single occasions for arthritis, one was a single epidural injection for back pain, and three were short courses of oral steroid for respiratory illness, back pain, and degenerative arthritis.

Reviewer comment: *These medications were used in small doses and/or short courses in few subjects, and would not be expected to have significantly impacted the overall immunogenicity results of the study.*

8.1.3.2.2 Immunogenicity Endpoints

Primary Immunogenicity Non-inferiority Endpoints

- The difference in the SCR or a 4-fold rise in HAI titer at Day 28 between Flublok and Fluzone for each vaccine strain in subjects ≥ 65 years of age was one of the two primary non-inferiority endpoints. These data are presented in Table 39. The Applicant also evaluated whether the LB of the 95% CI on SCRs met FDA guidance criteria for immune response (not the primary endpoint).

Table 39 Difference in Seroconversion/4-Fold Rise in HAI Titers between Flublok and Fluzone at Day 28 in Subjects ≥65 years of age – Evaluable Population – PSC03

Strain	Parameter	Flublok n=431 %	Fluzone n=430 %
A/New Caledonia (H1)	SCR	43	33
A/New Caledonia (H1)	UB of [SCR TIV – SCR Flublok]*	-4.4	-4.4
A/New Caledonia (H1)	Meets non-inferiority criteria?	Yes	Yes
A/New Caledonia (H1)	LB of the 2-sided 95% CI for SCR	38.7	28.1
A/New Caledonia (H1)	Meets immune response criteria?***	Yes	No
A/Wisconsin (H3)	SCR	78	58
A/Wisconsin (H3)	UB of [SCR TIV – SCR Flublok]*	-13.9	-13.9
A/Wisconsin (H3)	Meets non-inferiority criteria?	Yes	Yes
A/Wisconsin (H3)	LB of the 2-sided 95% CI for SCR	73.5	52.8
A/Wisconsin (H3)	Meets immune response criteria?***	Yes	Yes
B/Ohio (B strain)	SCR	29	39
B/Ohio (B strain)	UB of [SCR TIV – SCR Flublok]*	16.1	16.1
B/Ohio (B strain)	Meets non-inferiority criteria?	No	No
B/Ohio (B strain)	LB of the 2-sided 95% CI for SCR	25.0	34.4
B/Ohio (B strain)	Meets immune response criteria?***	No	Yes

Source: Table 14.2.2.1, Module 5, Volume 10, pp176-177

SCR=seroconversion or 4-fold rise in HAI titer to at least 1:40

LB= lower bound of the 2-sided 95% CI

*Upper bound (UB) 2-sided 95% CI of the difference between SCR for Fluzone minus Flublok should not exceed 10%.

**FDA immune response criteria: LB of the 2-sided 95% CI for SCR should meet or exceed 30%.

Reviewer comment: Flublok met pre-specified criteria for immune response and non-inferiority for both the H1 and H3 strains, but non-inferiority was not demonstrated for the B strain. The Applicant stated that the immune response to the B strains was not an equal comparison because Flublok contained the B/Ohio antigen and Fluzone contained the B/Malaysia antigen. However, the Applicant did not test their hypothesis by comparing immune responses elicited when HA antigens derived from each of the two B strains was used in the HAI assay. While it may be theoretically possible that the difference in antigen strains contributed to the difference in immune responses, these antigens are considered related by the WHO reference laboratories and interchangeable for purposes of vaccine production, and the reviewer therefore believes that differences in immune responses elicited by the two strains should not have been significantly different.

- The GMT ratio of Fluzone to Flublok at Day 28 for each vaccine strain was the second non-inferiority co-primary endpoint for study PSC03. The results of these analyses are presented in Table 40.

Table 40 GMT Ratios Day 28 – Evaluable Population - PSC03

Visit	Strain	H1	H3	B strain
Day 0 GMT	Fluzone n=430	70.2	44.7	80.3
Day 0 GMT	Flublok n=431	69.0	42.7	79.9
Day 28 GMT	Fluzone n=430	148.1	199.2	194.8
Day 28 GMT	Flublok n=431	176.8	338.5	149.6
Day 28 GMT	UB GMT Fluzone/ GMT Flublok	0.86	0.60	1.34
Day 28 GMT	Meets non-inferiority Criteria?*	yes	yes	yes

Source: Table 14.2.1.1, Module 5, Volume 10, p165.

*FDA criteria for non-inferiority: the upper bound (UB) of the 2-sided 95% CI on the GMT ratio GMT Fluzone/GMT Flublok should not exceed 1.5.

Reviewer comment: *Flublok met 5 of the 6 primary endpoint criteria for demonstrating non-inferiority to Fluzone. The H1 and H3 antigens met both non-inferiority endpoints. The B strain demonstrated non-inferiority to Fluzone by GMT ratio but not by SCR criteria.*

Secondary Immunogenicity Endpoints

- The proportion of subjects in each vaccine group achieving a post-vaccination HAI antibody titer at Day 28 of $\geq 1:40$ or greater to each vaccine antigen was a pre-specified secondary immune response endpoint (Table 41).

Table 41 Proportion with HAI $\geq 1:40$ at Day 28 – Evaluable Population PSC03

Strain	Parameter	Flublok N=431	Fluzone N=430
H1	% HAI $\geq 1:40$ at Day 28, n(%)	408 (95)	408 (95)
H1	LB*	(92.1)	(92.4)
H1	Pass?*	Yes	Yes
H3	% HAI $\geq 1:40$ at Day 28, n(%)	416 (97)	398 (93)
H3	LB*	(94.3)	(89.7)
H3	Pass?*	Yes	Yes
B	% HAI $\geq 1:40$ at Day 28, n(%)	395 (92)	418 (97)
B	LB*	(88.6)	(95.2)
B	Pass?*	Yes	Yes

Source: Table 14.2.3.1 Module 5, Volume 10, pp198-199.

n=number of subjects with post-vaccination HAI titer $\geq 1:40$.

*LB = lower bound of the 2-sided 95% CI

**PASS = proportion of subjects in each vaccine group achieving a post-vaccination HAI antibody titer (Day 28) of $\geq 1:40$ or greater to each vaccine antigen should meet or exceed 60%.

Reviewer comment: *For the proportion of subjects with a post-vaccination HAI titer of $\geq 1:40$ at Day 28, both Flublok and Fluzone exceeded the pre-specified immune response criteria for all three antigen strains.*

- The Applicant also performed exploratory analyses on EOIS immune response data and found that immune responses waned in a similar fashion between the treatment groups (data not shown).

Site 5: Post-hoc Immunogenicity Analyses

Reviewer comment: *The Applicant performed post hoc primary and secondary immunogenicity analyses on subjects from Site 5 (n=126) where study staff had access to the randomization code and where vaccine had been improperly disposed of (deviations in GCP). According to the Applicant's report, the data did not differ significantly between Site 5 and the remaining sites. Overall, the post hoc analyses performed by the Applicant suggested that access of study site personnel to the randomization code with potential for breaking of the blind at Site 5 did not significantly bias the overall results of study PSC03. In particular, the efficacy results do not appear to have been impacted. The reviewer also acknowledges that access of study site staff to the randomization code should not have affected HAI results because all laboratory personnel who performed these assays remained blinded. As a result, the Applicant included data from Site 5 in the pre-specified analyses for study PSC03. The statistical reviewer agreed that, based on review of sensitivity analyses, data from Site 5 could be pooled with the rest of the study population.*

Efficacy Endpoints

Results of the assessment of Flublok efficacy endpoints are presented in Table 42.

Table 42 Clinical Efficacy of Flublok relative to Fluzone – Evaluable Population – PSC03

Treatment Group	Flublok n=436	Fluzone n=433
NS/TS collected n(%) *	25 (5.8)	28 (6.5)
Subjects with positive NS/TS culture	1 (0.2)	2 (0.5)
Relative Efficacy (RE)**	50.23	n/a
95% CI	(-446.9, 95.47)	n/a
%RR ratio Flublok/TIV	49.77	n/a
95% CI	(4.53, 546.86)	n/a
Subjects with culture- Confirmed CDC-ILI	1 (0.2)	2 (0.5)
Relative Efficacy	50.23	n/a
95% CI	(-446.9, 95.47)	n/a
%RR ratio	49.77	n/a
95% CI	(4.53, 546.86)	n/a
Subjects with CDC-ILI symptoms regardless of culture results	27 (6.2)	28 (6.5)
Relative Efficacy	4.02	n/a
95% CI	(-60.09, 42.45)	n/a
%RR ratio	95.98	n/a
95% CI	(57.55, 160.09)	n/a

Source: Table 14.2.5, Module 5, Volume 10, p222

*NS/TS=nasal swab/throat swab for influenza culture

**Relative Efficacy (RE)= (1 – RR) x 100

$$***\%RR = (\%Flublok \text{ positive} / \%Fluzone \text{ positive}) \times 100$$

n/a = not applicable

- Overall, 53 sets of cultures were taken, 28 Fluzone and 25 Flublok recipients. Of these, only 3 were positive, 2 Fluzone and 1 Flublok, all three for influenza Type A. For both endpoints of culture-confirmed CDC-ILI and culture-positive NS/TS regardless of symptoms, relative protective vaccine efficacy was calculated as 50.23% for Flublok versus Fluzone. For the secondary endpoint of CDC-ILI symptoms regardless of culture results, relative VE of Flublok to Fluzone was 4.02%.

Reviewer comment: The number of cases of respiratory illnesses, CDC-ILI, and positive NS/TS cultures for influenza in this study were too small and confidence intervals too wide to draw conclusions regarding non-inferiority or relative protective vaccine efficacy of Flublok to Fluzone.

Immunogenicity and Efficacy Conclusions PSC03

- Vaccination of adults ≥ 65 years of age with a single dose of trivalent rHA vaccine 135 μ g elicited an immune response which met 5 of the 6 primary endpoint acceptance criteria for demonstrating non-inferiority to a U.S. licensed TIV using GMT ratios and difference in seroconversion/significant increase rates as suggested in the May 2007 FDA Guidance document. Flublok demonstrated non-inferiority to Fluzone by these criteria to the H1 and H3 antigen strains contained in the vaccine. In evaluating the B strain, Flublok demonstrated non-inferiority to Fluzone by GMT ratio criteria, but not when the difference in rates of seroconversion/significant increase was used to assess non-inferiority.
- Flublok met all three pre-specified secondary endpoint criteria for the proportion of subjects with HAI titers $\geq 1:40$ at Day 28. Both vaccine groups greatly exceeded FDA criteria for all three strains including the B strain. By EOIS the proportion of subjects with a persistent HAI titer $\geq 1:40$ declined for all three strains in a similar fashion for both treatment groups.
- Overall, the immunogenicity results in this study suggest that Flublok elicits strong immune responses to H1 and H3, and that these responses are non-inferior to Fluzone. Responses to the B strain were lower for both treatment groups, and non-inferiority of Flublok to Fluzone could not be established. The clinical significance of this is not clear, particularly in view of good “seroprotection rates” (% HAI $\geq 1:40$ on Day 28). This pattern has been noted for other licensed TIVs. Additionally, concerns related to the HAI assay and the interpretation of HAI titers obtained using BEVS-derived antigens persist and will be addressed in Sections 9 and 12.
- Evaluation of the relative protective efficacy of Flublok to Fluzone could not be adequately assessed because the attack rate was $<1\%$ and the sample size too small.

8.1.3.2.3 Safety Outcomes

- The Safety Population was comprised of all 869 subjects who received a single injection of Study Vaccine including 436 subjects in the Flublok group and 433 subjects in the Fluzone group.
- Summary statistics consisting of frequency counts and percentages were used to report reactogenicity events. Treatment-emergent adverse events (Unsolicited AEs) were tabulated and categorized by SOC and PT. The study was not powered to detect differences in specific AEs between the study groups, but the chi-square test was used to detect significant differences.
- Subjects with missing data were not imputed, and were excluded from the denominator when calculating the percentage of subjects with specific AEs. Any event with missing severity data was assumed to be severe, and any event with missing causality data was assumed to be related to the vaccine.
- The Safety Review was conducted from the source data, the Applicant's tables and line listings, and the electronic datasets, and will be descriptive in nature.

Deaths and Serious Adverse Events

- There were a total of 87 SAEs occurring in 70 subjects, including four deaths reported by the Applicant in this study. None were assessed by the investigators as being related to the study vaccines.

Reviewer comment: Narrative summaries and CRFs for the SAEs were reviewed. All were assessed as not related to the study vaccines. No apparent trends or unusual patterns were noted. The Applicant provided detailed summaries of these events, and the reviewer agrees that, given the information provided, these events appear unrelated to the study vaccine. Although assessed as not related to the study vaccine, the 2 deaths are summarized briefly below:

- Perforated Viscus with Secondary Peritonitis (Fatal) Subject 3027, Flublok - an 80 year old Caucasian female received Flublok on ----(b)(6)-----. Four days later, on ----(b)(6)----, she presented to the ER with an acute abdomen due to perforated diverticulum and peritonitis. She underwent a laparotomy and bowel resection, but died from septic shock and multi-organ system failure. Pathology report confirmed perforated diverticulosis of the recto-sigmoid colon and peritonitis.

Reviewer comment: This fatal SAE does not appear to be related to the study vaccine.

- Pontine hemorrhage (Fatal), Subject 1017, Flublok – an 89 year old Caucasian female received Flublok on ----(b)(6)-----. During the week following vaccination, she reported tiredness/lack of energy and fatigue, but no additional AEs were reported until an acute change in mental status on ----(b)(6)-----. She was admitted to a hospital with a diagnosis of intraparenchymal pontine hemorrhage and allowed to expire. She had a history of hypertension and was also taking an anti-platelet medication prior to this event.

Reviewer comment: *This fatal SAE does not appear to be related to the study vaccine.*

Discontinuations Due to Adverse Events

- No subjects in the Flublok group were discontinued from the study due to an AE.
- One subject in the Fluzone group was discontinued 42 days post-vaccination after experiencing a large right intracerebral hemorrhage. This SAE was assessed as not related to Fluzone.

Unsolicited Adverse Events (Treatment-emergent) According to Severity and Vaccine Relatedness

Unsolicited AE's (treatment-emergent AEs) occurring from Day 0 through Day 28 according to treatment group, severity, and vaccine-relatedness are presented in Table 43. Reactogenicity events were included as treatment-emergent events in this analysis if the event(s) occurred within 15 minutes of vaccination, persisted beyond Day 7, or were first reported after Days 0-7.

Table 43 Summary of Unsolicited AEs According to Severity and Relationship to Vaccine by Treatment Group – Safety Population (Applicant's Report) – PSC03

Category	Severity or relatedness*	Fluzone n=433 n (%)	Flublok n=436 n (%)
Subjects with at least one AE regardless of causality	All severity grades**	85 (20)	90 (21)
Subjects with at least one AE regardless of causality	Mild	51 (12)	54 (12)
Subjects with at least one AE regardless of causality	Moderate	25 (6)	30 (7)
Subjects with at least one AE regardless of causality	Severe	9 (2)	6 (1)
Serious AEs (regardless of causality)	All SAEs	34 (8)	36 (8)
Serious AEs (regardless of causality)	Deaths	2 (<1)	2 (<1)
Vaccine relationship	Not related	62 (14)	61 (14)
Vaccine relationship	Related	10 (2)	16 (4)
Vaccine relationship	Unknown	13 (3)	13 (3)

*Causality as assessed by the investigator.

**Denominator includes all subjects with AEs regardless of causality.

Subjects with multiple AEs in the same body system were counted once per SOC and once per PT using the event with the strongest relationship to the study vaccine.

Source: Tables 14.3.1.1, p223, 14.3.1.4, p235, 14.3.1.7, p274, 14.3.1.10, p308, Module 5, Volume 10.

- The proportion of subjects who reported AEs was similar in each treatment group, 21% of Flublok subjects and 20% of Fluzone subjects. Both treatment groups reported SAEs with equal frequencies of 8%, and 2 deaths occurred in each treatment group. With regard to vaccine relationship, AEs were categorized as not related, related or as unknown relationship. Most events were considered not related. More Flublok than Fluzone recipients experienced AEs that were assessed as vaccine-related (4% vs 2%).

Reviewer comment: *The assessment of vaccine relationship differs from that used in studies PSC04 and PSC06 where relationship was categorized as not related, possibly related or related. The “unknown” category in PSC03 appears to be analogous to the “possibly related” category in the other two studies.*

Reviewer comment: *The reviewer determined rates of Unsolicited treatment-emergent AEs according to severity, attribution, and treatment group based on evaluation of the electronic datasets and obtained results nearly identical to the Applicant’s report. Discrepancies between the reviewer’s findings and the Applicant’s report were satisfactorily explained in the Applicant’s April 7, 2009 CR, Item 21 a.*

Severe Unsolicited Adverse Events

Table 44 summarizes the 29 AEs categorized as severe that occurred in the 26 Flublok subjects through Day 180 found by the reviewer in the electronic datasets.

Table 44 Severe Unsolicited AEs – Safety Population, Flublok Group – PSC03

Subject ID	Age/ Race*	Sex	Preferred term/comments	Vax Date	Onset	Outcome/ Relatedness**
0041	73	M	Rt popliteal artery aneurysm	11/2/06	1/24/07	1§
0050	71	F	Breast cancer metastatic	11/8/06	12/4/06	Ongoing
0052	75	M	Worsening Congestive heart failure	11/8/06	5/8/07	2§
0052	75	M	Pulmonary embolism	11/8/06	5/21/07	2
0055	81	M	Gastroenteritis	11/8/06	2/7/07	1
0063	79	M	Bronchitis acute	11/10/06	2/19/07	1
0505	67	F	Adenocarcinoma	10/11/06	3/21/07	2
0537	75	F	Myocardial infarction	10/18/06	1/24/07	2
0593	66	F	Nasopharyngitis/ Cold symptoms	11/15/06	12/9/06	1**
0639	82	F	Appendicitis	12/4/06	3/25/07	1
0763	66	F	Injection site swelling/9 cm	11/1/06	11/1/06	1**
1017	89	F	Pontine brain stem haemorrhage	10/13/06	1/13/07	Fatal
1022	82	F	Cholecystitis acute	10/13/06	4/18/07	1
1022	82	F	Pulmonary embolism	10/13/06	4/21/07	1
1075	67	M	Pancreatitis	10/20/06	3/25/07	1
1082	68	F	Lower gastrointestinal haemorrhage/post total colectomy	10/21/06	2/28/07	1
1107	67	F	Meniscus tear, Left	10/23/06	2/27/07	1
1196	75	M	Anxiety (hospitalized)	11/09/06	2/21/07	1
1204	66	M	Renal failure acute/due to IgA nephropathy	11/10/06	3/19/07	1
1214	66	M	Myocardial infarction	11/16/06	11/22/06	1
1288	65	F	Tooth infection/root canal	11/1/06	11/21/06	1
1307	66	M	Coronary artery disease	11/13/06	3/20/07	1
1528	78	F	Osteoarthritis/left knee DJD	10/12/06	1/30/07	1
1580	88	F	Syncope vasovagal	11/1/06	11/14/06	1
1615	78	M	Traumatic brain injury	11/14/-6	2/2/07	2
2122	88	M	Barrett's oesophagus	11/17/06	4/23/07	2
2122	88	M	Renal failure acute/due to outflow obstruction	11/17/06	3/29/07	1
3027	80	F	Perforated viscus with secondary	11/2/06	11/6/06	Fatal

Subject ID	Age/ Race*	Sex	Preferred term/comments	Vax Date	Onset	Outcome/ Relatedness**
			peritonitis			
3034	70	M	Atrial fibrillation	11/3/06	5/10/07	2

*All subjects were White/Caucasian

**Subjects #0593: AE was considered unknown relationship to study vaccine.

Subject #0763: AE was considered related to study vaccine.

All other subjects' AEs were assessed as not related to the study vaccine.

§ 1 = resolved without sequelae; 2 = resolved with sequelae

Source: Review of electronic datasets

Reviewer comment: *All of the severe AEs listed in the table with the exception of Subject #s 0593 (nasopharyngitis), 0763 (injection site swelling), and 1288 (tooth infection) were also considered SAEs. Narrative summaries and CRFs provided by the Applicant were reviewed. Only Subject 0793, injection site swelling, appeared to have a related severe AE. Subject 0593, nasopharyngitis, was assessed as unknown relatedness to the vaccine, but the onset of symptoms followed vaccination by 24 days and, in the reviewer's opinion, may have been unrelated. The remaining 27 severe AEs do not appear to have been related to Flublok.*

Events that Occurred in Fewer than 0.5% of Subjects but of Potential Interest

Although individual AEs were reported at low frequency, the datasets were examined more closely for safety signals, in particular for autoimmune or hypersensitivity phenomena, and for idiosyncratic reactions that have been reported following immunization with a variety of vaccines. Review of nervous system disorders, immune system disorders, musculoskeletal and connective tissue disorders, and blood and lymphatic disorders did not identify findings suggestive of a safety signal in any of these categories.

- **Rash:** Two Flublok subjects had rashes that were ongoing at the time of the interim analysis. Subject #0572 experienced a facial rash that was considered mild, non-serious, and not related to the vaccine. Flublok Subject #1086 had eczema, also non-serious, mild, and assessed as not related to the vaccine. Remaining three cases were: ingrown toenail, sebaceous cyst, and blisters from topical antibiotic. All were assessed as unrelated to Flublok.

Reviewer's comment: *The reviewer concurs that these events were not likely to have been related to receipt of Flublok.*

- **Oculorespiratory Syndrome:** Search of the datasets for the terms "conjunctivitis" and "red eyes" yielded one Flublok recipient, #1159 and one Fluzone recipient, #1521, who reported conjunctivitis. Flublok subject #1159 reported the onset of conjunctivitis without other symptoms suggestive of ORS 4 days post-vaccination. The Fluzone recipient had onset of conjunctivitis 12 days post-vaccination, accompanied by headache. Neither of these cases fit the definition of ORS.

- The Applicant was asked specifically to provide narratives and CRFs for any subject who experienced severe (Grade 3) rash, hypersensitivity of any intensity/severity grade, or pregnancy. The Applicant replied that no additional events of this type occurred during this study.

Unsolicited Adverse Events that Occurred in $\geq 0.5\%$ of Subjects

The Applicant submitted an analysis of all Unsolicited AEs that occurred from Day 0 through Day 28 in at least 0.5% of subjects regardless of causality according to MedDRA SOC and PT. The Applicant's tables were confirmed by review of the electronic datasets. Overall, the frequency of Unsolicited AEs was low and without important imbalances between treatment groups.

- Injection site erythema (2.3%) was the most frequently reported AE among Flublok recipients, followed by injection site hemorrhage and sinusitis, each 1.4%. Injection site swelling, diarrhea and URI were slightly less frequent, each 1.1%. The most notable difference between the treatment groups was the greater frequency of local injection site reactions among the Flublok recipients.

Reviewer's comment: The Applicant's report of subjects with Unsolicited AEs by SOC was compared to the Medical Officer's results from review of the electronic datasets. The number of subjects found in the electronic datasets as reporting AEs in each SOC category was identical to the Applicant's report, with no important imbalances found between the two treatment groups.

Review of Unsolicited Adverse Events according to Severity Grade

Unsolicited AEs that occurred with a frequency of $\geq 0.5\%$ regardless of causality were assessed according to severity grade (data not shown).

Reviewer comment: Among Unsolicited AEs occurring with a frequency of $\geq 0.5\%$, the frequencies of events according to severity grade were similar between the two treatment groups. Most events were mild or moderate in severity. No unusual pattern of severe Unsolicited AEs was observed. The data found in the electronic datasets was identical to the Applicant's report.

Review of Unsolicited Adverse Events and Relationship to Study Vaccine

The Applicant provided data summarizing all treatment-emergent Unsolicited AEs that were considered to be related or of unknown relationship to the study vaccines according to SOC and PT (Table 23, Module 5, Volume 10, p77 ; source Table 14.3.1.4, pp235-251 – data not shown). A total of 23 (5.3%) Fluzone and 29 (6.6%) Flublok subjects had Unsolicited AEs assessed as either related or of unknown relationship to the study vaccine. The most frequently reported treatment-related AEs by treatment group were:

- Flublok: injection site erythema (2.3%), injection site hemorrhage (0.9%), injection site swelling (1.1%), and nasopharyngitis (0.7%)
- Fluzone: injection site hemorrhage (0.7%).

Reviewer comment: *With the exception of local injection site reactions which occurred more frequently in the Flublok group and which were felt to be related to the study vaccine, there were no other imbalances between the treatment groups. Overall, relatively few AEs were assessed as related or of unknown relationship to the study vaccine.*

8-Day Solicited Reactogenicity Events (Day 0 – Day 7)

Table 45 presents reactogenicity events by treatment group. Data is shown only for all events (mild, moderate or severe) and severe events within each category. The reviewer confirmed the Applicant's results for all events assessed as Grade 2 or Grade 3 (moderate or severe) by evaluation of the electronic datasets.

Table 45 Solicited Local and Systemic Reactogenicity Events within 8 Days of Vaccination by Treatment Group and according to Severity – Safety Population - PSC03

Solicited AE	Severity Grade*	Fluzone n=433 Dataset	Fluzone n=433 Applicant	Flublok n=436 Dataset	Flublok n=436 Applicant
N (%) with any reaction	Grade 0	--	216 (50)	--	226 (52)
N (%) with any reaction	Grade 1	--	173 (40)	--	162 (37)
N (%) with any reaction	Grade 2	--	31 (7)	--	37 (8)
N (%) with any reaction	Grade 3	--	13 (3)	--	8 (2)
Injection site bruising	Any (Grade 1,2,3)	--	22 (5)	--	15 (3)
Injection site bruising	Grade 3	1	1 (<1)	0	0
Injection site pain	Any (Grade 1,2,3)	--	100 (23)	--	94 (22)
Injection site pain	Grade 3	0	0	0	0
Hard swelling	Any (Grade 1,2,3)	--	17 (4)	--	13 (3)
Hard swelling	Grade 3	4	1 (<1)	2	3 (<1)
Redness	Any (Grade 1,2,3)	--	54 (12)	--	44 (10)
Redness	Grade 3	6	6 (1)	2	2 (<1)
Soft swelling	Any (Grade 1,2,3)	--	41 (9)	--	33 (8)
Soft swelling	Grade 3	4	4 (1)	2	2 (<1)
Fatigue	Any (Grade 1,2,3)	--	42 (10)	--	40 (9)
Fatigue	Grade 3	1	1 (<1)	1	1 (<1)
Headache	Any (Grade 1,2,3)	--	41 (9)	--	46 (11)
Headache	Grade 3	0	0	0	0
Joint pain	Any (Grade 1,2,3)	--	25 (6)	--	22 (5)
Joint pain	Grade 3	0	0	0	0
Muscle pain	Any (Grade 1,2,3)	--	38 (9)	--	32 (7)
Muscle pain	Grade 3	0	0	1	1 (<1)
Nausea	Any (Grade 1,2,3)	--	15 (3)	--	19 (4)
Nausea	Grade 3	1	1 (<1)	0	0
Shivering	Any (Grade 1,2,3)	--	16 (4)	--	16 (4)
Shivering	Grade 3	0	0	1	1 (<1)
Sweating	Any (Grade 1,2,3)	--	7 (2)	--	11 (3)
Sweating	Grade 3	0	0	0	0
Tiredness, lack of energy	Any (Grade 1,2,3)	--	65 (15)	--	65 (15)
Tiredness, lack of energy	Grade 3	1	1 (<1)	1	1 (<1)
Fever	Any fever: ≥100.4°F ≥38°C	0	0	1	1 (<1)
Fever	Severe ≥102.2°F	0	0	0	0

*subjects with multiple symptoms in the same category were counted once per category using the symptom with the maximum grade.

-- indicates that the value was not evaluated by the reviewer

Grading scale for measured injection site reactions (redness, induration):

- Grade 0= measured <10mm
- Grade 1= measured ≥10mm and < 20mm
- Grade 2= measured ≥20mm and <50mm
- Grade 3= measured ≥50mm.

Functional scale used by subjects for self-assessment of reactogenicity :

- Grade 0= didn't have it at all
- Grade 1= noticed it, but it didn't interfere with usual activities at all
- Grade 2= had it, and it was bad enough to prevent a significant part of usual activities
- Grade 3= had it, and it prevented most or all of normal activities, or had to see a doctor for prescription medicine.

Source: Tables 14.3.6.1 and 14.3.6.3, Module 5, Volume 10, pp349 and 353-355, and electronic datasets.

- Approximately 50% of subjects in each treatment group experienced some type of reactogenicity event. Most events were assessed as mild. There were very few moderate or severe events. Flublok recipients reported 37% mild, 8% moderate and 2% severe reactogenicity events. Fluzone recipients reported 40% mild, 7% moderate, and 3% severe events. The most frequently reported events were: local injection site pain (Flublok 22% and Fluzone 23%), tiredness/lack of energy (Flublok 15% and Fluzone 15%); headache (Flublok 11% and Fluzone 9%) and fatigue (Flublok 9% and Fluzone 10%). Overall, the frequencies and severity of both local and systemic reactions were similar between treatment groups. Almost all events resolved spontaneously by Day 7.
- Only one subject was documented as having fever in the 8 days following vaccination. The datasets revealed that Subject #2076 received Flublok on November 1, 2006 and was afebrile until November 6, 2006, Day 5, when he experienced a fever of 101.3°F. He appeared to defervesce thereafter, and, on Day 7, had a temperature recording of 99.3°F.

Safety Results Site 5

- The safety data suggested that reporting of reactogenicity events was somewhat higher for Flublok as compared to Fluzone at Site 5 than for the remaining sites, in particular for tiredness/lack of energy (14% vs 10% respectively) and for headache (8% vs 5%). Overall, Unsolicited AEs were reported at a lower rate at Site 5 (6.3%) than at the remaining sites (22.5%), but there were no apparent differences in frequencies or severity among individual AEs between the Flublok and Fluzone groups. There were no apparent trends or unusual differences in SAE reporting among the sites.

Reviewer comment: Some differences in reporting might be attributed to the greater mean age of subjects at Site 5 (Flublok 79.1 yrs) versus the remaining sites (Flublok 71.9 yrs).

Pregnancies

There were no pregnancies reported from Day 0 through Day 28 in either treatment group during the study.

Discontinuations Due to Adverse Events

There was one discontinuation due to an AE in the study. This occurred in a Fluzone recipient #1079, a 73 year old female who was hospitalized with a large right cerebral hemorrhage, assessed as not likely to be related to the study vaccine. No Flublok recipients were discontinued due to an AE.

Case Report Forms Reviewed for Study PSC03

CRFs were reviewed for the 70 subjects who experienced SAEs. None of these cases were assessed as being related to the study vaccine. There were no other unusual events that appeared indicative of a safety signal or that warranted further investigation.

Vital signs

There were no unexpected treatment-emergent trends or patterns in vital signs identified following Flublok administration in study PSC03.

Laboratory Evaluation

There were no routine clinical laboratories performed for the study other than screening urine pregnancy tests.

8.1.3.3 Comments Study PSC03: Safety Conclusions

- No vaccine-related deaths or SAEs occurred in the study, and no Flublok recipients discontinued the study due to adverse events. The number and type of SAEs were similar between treatment groups, and were not unusual or unexpected for an elderly population.
- Approximately 50% of subjects in each treatment group experienced some type of reactogenicity event between Days 0 and 7. The majority of events were mild in intensity and occurred with similar frequencies between the two treatment groups. The most frequent reactions reported by Flublok recipients were: injection site pain (22%); tiredness/lack of energy (15%); headache (11%); and fatigue (9%). Almost all events resolved spontaneously by Day 7. There was no evidence of unusual hypersensitivity reactions among the Flublok recipients.
- The frequencies of Unsolicited AEs were low without great imbalances between treatment groups. Most Unsolicited AEs fell in one of two SOC categories: Infections and Infestations (6% of subjects in both groups) and General Disorders and Administration Site Disorders (Fluzone 3% vs Flublok 4%). The most notable difference between the treatment groups was the greater frequency of local injection site reactions (after Day 7) among the Flublok recipients. Injection site erythema (2.5%) was the most frequently reported AE among Flublok recipients, followed by injection site hemorrhage and swelling, nasal congestion and sinusitis, each 1.4%. The majority of events were mild in intensity and were considered unrelated to the vaccine. Overall, there were no important imbalances between the two treatment groups.

8.1.3.4 Comments Study PSC03: Safety and Efficacy Conclusions

- Overall, Flublok appeared well-tolerated in this study without apparent unusual patterns of adverse reactions. The 135µg dose elicited an immune response that met non-inferiority criteria for the H1 and H3 strains, and the proportion of subjects with HAI titers $\geq 1:40$ at Day 28 exceeded immune response criteria for all three vaccine strains. The B strain, however, failed to meet the non-inferiority endpoint for the difference in SCRs/4-fold increase in HAI titer. Additionally, concerns related to the HAI assay including the interpretation of HAI titers obtained when using BEVS-derived antigens persist and will be addressed in Sections 9 and 12. Assessment of the relative efficacy of Flublok to Fluzone could not be adequately assessed in this study because the infection rate was less than one percent and the sample size too small.

8.1.4 Trial #4

8.1.4.1 Applicant's Protocol Number PSC01 (BB-IND 11951) "Evaluation of the Immunogenicity and Safety of Two Preparations of Trivalent Recombinant Baculovirus-expressed Hemagglutinin Influenza Vaccine Administered Intramuscularly in Healthy Adults Aged 18-49 Years."

8.1.4.1.1 Objective/Rationale:

Primary Objective:

- The primary objective of this Phase 2 study was to evaluate the dose response and ability of two trivalent preparations of Flublok (75µg or 135µg total of rHA), as measured by single radial immunodiffusion assay (SRID), to induce a serological response (HAI antibodies) by comparing the proportion of individuals in each dose group who achieve a ≥ 4 -fold increase in HAI antibody titer by comparing Day 0 vs Day 28.

Reviewer comment: The Applicant reports that, in the original primary analysis, the lower limit of detection for the HAI assay used in this study was a titer of 1:4. Samples with undetectable titers were assigned a value of <1:4, (i.e., 1:2). Subjects whose baseline titers were undetectable and who had an HAI titer of $\geq 1:8$ (using a 2-fold dilution series) at Day 28 were considered to have a ≥ 4 -fold rise in titer ("seroconversion"). This differs from the CBER May 2007 Guidance for Industry, "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines" where "seroconversion" is defined as a post-vaccination titer of $\geq 1:40$ in subjects with undetectable baseline antibody or a ≥ 4 -fold rise in antibody in subjects with a baseline titer of $\geq 1:10$ (also using a 2-fold dilution series). To better approximate SCRs as defined in the CBER guidance, an exploratory analysis was conducted using a modified definition of seroconversion of $\geq 1:64$. The Applicant did not re-run the HAI antibody assay on banked sera, and conducted the exploratory analyses on existing HAI antibody data. The Applicant used an assay that, while validated and used in NIH-sponsored studies of influenza, is not equivalent to the assay used in the other studies submitted to the BLA. However, the Applicant selected a more conservative or stringent post-vaccination titer of $\geq 1:64$ which represents a 32-

fold rise in titer from the LOD <1:4 or 1:2. Additionally, any impact that the use of a different HAI assay might have on the entire study is expected to be small because this was a smaller and earlier phase study.

Secondary Objectives:

- To determine the safety, relative to placebo, of a single dose of Flublok containing a total of either 75µg or 135µg of rHA, as determined by the absence of clinically significant adverse events and the evaluation of local and systemic reactions.
- To determine the efficacy, relative to placebo, of a single dose of Flublok containing a total of either 75µg or 135µg of rHA in the prevention of laboratory documented (culture-confirmed) symptomatic influenza (as defined by the presence of CDC-ILI) due to strains represented in the vaccine.
- To determine the efficacy, relative to placebo, of a single dose of Flublok in the prevention of symptomatic or asymptomatic laboratory-documented influenza infection or illness due to influenza strains represented in the vaccine. In this analysis, asymptomatic infections were identified by means of a ≥ 4 -fold increase in HAI antibody titer by comparing titers at Day 28 vs Day 180.
- To assess the clinical efficacy of Flublok in the prevention of CDC-ILI, regardless of influenza culture results.
- To further evaluate post-vaccination antibody responses among the three study groups as a whole by calculating and comparing group-specific GMTs of serum HAI antibody titers on Days 0, 28, and 180.
- To assess whether there was a correlation between the level of post-vaccination HAI antibody on Day 28 with clinical protection against laboratory-confirmed influenza (as measured by culture-positivity or a ≥ 4 -fold rise in HAI antibody between Day 28 and Day 180).

Exploratory (Post-Hoc) Objectives:

- To assess whether Flublok meets the immunogenicity criteria listed in the May 2007 FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines,” namely:
 - SCR: Post-vaccination HAI titer of $\geq 1:40$ in subjects with undetectable baseline antibody or a 4-fold rise in antibody in subjects with a baseline HAI titer of $\geq 1:10$, with the achievement of post-vaccination HAI titer of at least 1:40. For adults < 65 years of age, the lower bound of the 2-sided 95% CI should meet or exceed 40%.
 - Proportion of subjects with a post-vaccination HAI titer of $\geq 1:40$. For adults <65 years of age, the lower bound of the 2-sided 95% CI should meet or exceed 70%.
- To assess the clinical efficacy of Flublok in the prevention of culture-positive influenza infection, regardless of whether the subject met the definition for CDC-ILI.

Reviewer’s comment: Only selected data from exploratory (post-hoc) efficacy endpoints will be presented or discussed in this review.

8.1.4.1.2 Design Overview

- PSC01 was a Phase 2, prospective, randomized, double-blinded, placebo-controlled, multi-center, dose-finding trial designed to obtain evidence of safety and immunogenicity and to determine the optimal dose, protective efficacy, and effectiveness of two formulations of Flublok relative to placebo in a population of healthy adults.
- A total of 460 subjects at three study sites were randomized in a 1:1:1 ratio to one of three treatment groups:
 - Flublok total 75µg rHA
 - Flublok total 135µg rHA
 - Placebo (normal saline for injection, USP)
- Subjects received a single injection of Flublok or placebo. Solicited AEs were collected for 7 days, Unsolicited AEs for 28 days, and SAEs for 6 months post-vaccination. Serologies were collected on Days 0 and 28.. Study Period
 - First subject enrolled: November 17, 2004.
 - Last subject completed: May 26, 2005.
- Dose selection: the Applicant states that previous studies of Flublok involved approximately 550 subjects vaccinated with either monovalent or bivalent formulations and an additional 325 subjects who received trivalent formulations. Results of these studies indicated that doses of Flublok up to 135µg in healthy young adults and up to 404µg in elderly adults were well-tolerated and not associated with greater reactogenicity or AEs than other TIVs. These previous studies also indicated that immune responses to doses of 45 to 135µg of HA were greater than or equal to responses elicited by TIV.
- A centralized laboratory blinded to the source of specimens conducted all serologic testing.

8.1.4.1.3 Population

- 460 healthy, medically stable adult males and females 18-49 years of age who met inclusion/exclusion criteria.
- Noteworthy exclusion criteria were the same as reported in the previous trials.

8.1.4.1.4 Products Mandated by the Protocol

- Flublok was administered as a single dose of 0.5mL of either 75µg or 135µg total rHA as determined by SRID IM into the non-dominant deltoid muscle.
- The 75µg dose of Flublok contained HA representing the three strains of influenza virus recommended by the WHO for the 2004-2005 influenza season:
 - 15µg A/New Caledonia/20/99 (H1N1)
 - 45µg A/Wyoming/3/03 (H3N2)
 - 15µg B/Jiangsu/10/03 (B strain)

Lot number 50-04011B

Reviewer comment: The lower 75µg dose of Flublok actually contained an equivalent amount of H3 antigen as the 135µg dose. This was taken into consideration when reviewing the immunogenicity results.

- The 135µg dose of Flublok contained the same HA antigens at the following doses:
 - 45µg A/New Caledonia/20/99 (H1N1)
 - 45µg A/Wyoming/3/03 (H3N2)
 - 45µg B/Jiangsu/10/03 (B strain)
- Lot number 50-04011A

Reviewer comment: The Applicant states that after formulation, it was determined that the dose of H1 contained 35µg of rHA per 0.5mL dose instead of the target 45µg. This was taken into consideration when reviewing the immunogenicity results.

- Placebo consisted of normal saline for injection, USP, and was administered as a single dose of 0.5mL by IM injection in the non-dominant deltoid muscle.

8.1.4.1.5 Endpoints

Primary Safety Endpoints

- Frequency of local and systemic reactogenicity events (“solicited events”) in the 7 days following vaccination noted on the Diary Card.
- Frequency of AEs (“unsolicited” AEs) and SAE’s that occurred in the 28 days following vaccination as assessed on any follow-up visits or phone calls, through Day 180.
- SAEs occurring from Day 0 through the last visit EOIS Day 180.
- ILI-related AEs: suspected treatment failures that occurred in the 6-month follow-up period.

Primary Immunogenicity Endpoint

- The frequency of 4-fold or greater increases in serum HAI titer in Flublok recipients against viruses represented in the vaccine. Subjects with a titer below the LOD (<1:4) were assigned a titer of 1:2, and were considered to have seroconverted if their Day 28 titer was ≥ 1:8 (minimum 4-fold rise).

Pre-specified Secondary Efficacy/Effectiveness Endpoints

- Proportion of subjects in the Flublok and placebo groups who experienced culture-positive CDC-ILI.
- Proportion of subjects in both treatment groups with CDC-ILI regardless of culture results.
- Proportion of subjects with laboratory evidence of influenza infection, either positive culture or serologic rise in titer between Day 28 and Day 180, regardless of symptoms.

Exploratory (Post-hoc) Efficacy/Effectiveness Endpoints

- Proportion of subjects with culture-confirmed CDC-ILI caused by influenza A/H3N2.
- Proportion of subjects with a positive influenza culture, regardless of whether the subject met the case definition for CDC-ILI.

Exploratory (Post-hoc) Immunogenicity Endpoints and Acceptance Criteria

Reviewer comment: Because the FDA May 2007 Guidance Document immune response endpoints and acceptance criteria apply to an HAI assay with a LOD of 1:10 (with a 2-fold dilution series), while the HAI assay used in study PSC01 had a LOD of 1:4 (also with a 2-fold dilution series), the Applicant modified these parameters to better approximate whether Flublok met the endpoints specified in the Guidance:

- Modified SCR for each strain: Post-vaccination HAI titer of $\geq 1:64$ on Day 28 in subjects with a pre-vaccination HAI titer of $< 1:4$ (undetectable by the HAI assay used in this study), or a ≥ 4 -fold rise in HAI titer on Day 28 in subjects with a prevaccination titer of $\geq 1:4$, with a minimum Day 28 titer of 1:64.
- Modified definition for the proportion of subjects with a post-vaccination HAI titer of $\geq 1:40$ for each strain: The post-vaccination HAI titer was changed to 1:64. The Applicant also analyzed the data using a less conservative cut off of 1:32.
- Acceptance criteria for these modified endpoints were:
 - SCR: For each strain, the lower bound of the 2-sided 95% CI should meet or exceed 40%.
 - Proportion of subjects in the Flublok group who achieved a post-vaccination (Day 28) HAI titer of $\geq 1:64$: The lower bound of the 2-sided 95% CI should meet or exceed 70%.

Reviewer comment: A post-vaccination titer of 1:8 from a baseline of undetectable (1:2) would represent a 4-fold rise in titer. The Applicant selected a more difficult endpoint to achieve, a titer of $\geq 1:64$, as a criterion for successful seroconversion.

Safety Variables

- Relationship of AEs to study vaccine was described as definitely not; probably not; possible; probable; definite; unknown

Reviewer comment: These definitions are different from the other three studies submitted to the BLA, for example, in PSC03: Related, not related, and unknown. For purposes of comparison across studies in the BLA review, any AE that is not categorized as definitely not/not related or definite/related will be considered as one group of possible/probably not/unknown. Severity grade of AEs were categorized as mild, moderate or severe as in the other studies submitted to the BLA.

- Reactogenicity (solicited) events: the frequencies of local and systemic reactions for 8 days following vaccination (Day 0 through Day 7), noted on the subject Memory Aid and assessed on the Day 8 contact.
 - Local (injection site) reactions: local pain; bruising; redness; swelling; induration
 - Systemic reactions: fever; fatigue; tiredness/lack of energy; shivering; joint pain; muscle pain; headache; nausea; sweating

Reviewer comment: The severity grading scales for Solicited AEs were identical to those used in studies PSC03, PSC04 and PSC06.

8.1.4.1.6 Surveillance Monitoring

- Subjects were observed for 20 minutes for any immediate AEs following vaccination.
- Subjects were provided a diary card on Day 0 and were instructed to record any symptoms, temperature, and to measure the injection site on the day of vaccination and over the following 7 days.
- Subjects returned on Day 2 for an arm check and to assess for axillary adenopathy and for the presence of oculorespiratory syndrome.
- Subjects returned on Day 8 for an arm check and to review the diary card.
- Follow-up phone calls
 - Following the Day 28 visit, subjects completed a weekly flu symptoms card to record flu symptoms and any Unsolicited AEs. These were reviewed with study staff during weekly follow-up phone calls. If the total flu symptom score was ≥ 2 , subjects were to report to clinic for illness evaluation and NP culture.
- Flu surveillance: Active surveillance for influenza began when two or more positive cases were detected in the community or from a single study subject. Surveillance ended after three consecutive weeks without a positive sample from the community or study subjects unless CDC surveillance reported continued circulation due to a strain that had not already occurred at that study site. Flu surveillance for the individual subject ended upon completion of the day 180 visit.
- SAE Reporting
 - Events that met the definition of an SAE (previously defined in the BLA), that were considered severe, and required follow-up care, required the completion of an SAE form. These were submitted to the Applicant within 24 hours of site awareness of the event, to the IRB, and were entered onto the CRF.
- The Applicant states that regular monitoring of data by the Data Coordinating Center and independent audit occurred according to GCP/ICH guidelines.

8.1.4.1.7 Statistical Considerations

- Please see the statistical review.
- Randomization: the study originally planned to enroll 900 subjects. Subjects were randomized 1:1:1 using a block method with a block size of 6.
- Blind: The investigators, the Applicant, subjects, and serology laboratory were blinded to study treatment assignment. The pharmacist and staff members who administered the study vaccines were not blinded and were not involved in subject assessments.
- Safety Population: all randomized subjects who received any dose of Study Vaccine. The Safety Population was used for all safety analyses.
- Evaluable Population for Immunogenicity: all vaccinated subjects who met the study criteria and had titers taken at baseline and Day 28.

- Evaluable Population for Protective efficacy (VE): all vaccinated subjects that met the study entry criteria.
- Efficacy Analyses
 - Pre-specified analysis for the primary immunogenicity endpoint: LOD for HAI assay was 4. Samples measuring < 4 were assigned a titer of 2. Those subjects with baseline undetectable titers and post-vaccination HAI titers of ≥ 8 at Day 28 were considered to have had a ≥ 4 -fold increase in titer.
 - Post-hoc analyses of seroconversion and proportion with HAI titer $\geq 1:64$ were modified because of the dilutions used in the assay which differed from CBER guidance as previously explained.
 - Frequency count and percentage of subjects with or without a 4-fold or greater increase in titer were presented by treatment group and overall. Differences between the treatment groups were evaluated using a Chi-Square test.
- Illness Evaluation
 - Summary statistics were used to present the number of cases of CDC-ILI and results of NP cultures.
- Vaccine Efficacy
 - VE was calculated as $100 \times (1 - \text{relative risk of subjects having a positive culture for influenza})$.
 - $VE = 100 \times (1 - \text{Proportion of Flublok subjects with positive culture} / \text{Proportion of Placebo subjects with positive culture})$
- GMTs for HAI titers for Day 0, 28, and 180 were evaluated by a repeated measure ANOVA.
- Summary statistics were used to present safety data.
- Sample Size
 - Seroconversion: A sample size of 450 subjects, 150 per treatment group was selected to ensure that a 15% or greater difference in the SCR between treatment groups would be detected with an $\alpha=0.05$ and 80% power. This assumed that 60-80% of subjects would have a 4-fold rise in HAI titer.
 - Culture confirmation: a placebo attack rate from recent studies ranging from 1.9% to 13% per influenza season was used to calculate sample sizes required to detect a difference between placebo and vaccine groups with an $\alpha = 0.05$ and a power of 80%: Subjects who withdrew or who were terminated were not replaced.
- Changes in the Conduct of the Study or Planned Analyses
 - The original planned study population was changed from 900 to 460 subjects based on available funding.

8.1.4.2 Results: Study PSC01

8.1.4.2.1 Populations Enrolled and Analyzed

Subject Disposition

Subject disposition for study PSC01 is presented in Table 46.

Table 46 Subject Disposition – PSC01

Disposition	Flublok 75µg N=153 n(%)	Flublok 135µg N=153 n(%)	Placebo N=154 n(%)	Overall N=460 n(%)
Randomized	153 (100)	153 (100)	154 (100)	460 (100)
Vaccinated	151 (99)	153 (100)	154 (100)	458 (99)
Completed	148 (97)	151 (99)	152 (99)	451 (98)
Discontinued	5 (3)	2 (1)	2 (1)	9 (2)
Due to AE	0	0	0	0
Lost to Follow-up	1 (1)	1 (1)	2 (1)	4 (<1)
Withdrew consent	0	1 (1)	0	1 (<1)
Death	0	0	0	0
Randomized, not vaccinated	2 (1)	0	0	2 (<1)
Other	2 (1)	0	0	2 (<1)
-Incarcerated during the Study	1 (1)	NA	NA	1 (<1)
-Unable to contact during flu surveillance period	1 (1)	NA	NA	1 (<1)
Total Enrolled	153	153	154	460
Safety Population	151	153	154	458
-Randomized not vaccinated	2 (1)	0	0	2 (<1)
Evaluable Population (Protective Efficacy)	150	151	153	454
Received TIV	0	2 (1)	1 (1)	3 (<1)
Pregnancy	1 (1)	0	0	1 (<1)
Evaluable Population (Serology)	150	150	151	451
No 28 Day Titer	0	1 (1)	2 (1)	3 (<1)

Source: Table 14.1.1, Module 5, Volume 1, p85, and confirmed by evaluation of the electronic datasets.

- A total of 460 subjects were randomized, 458 were vaccinated, and 451 completed all study procedures.
- There were no deaths or discontinuations due to AEs during the study.

Reviewer comment: *Disposition of subjects did not differ greatly among the three treatment groups. More subjects in the Flublok 75µg group discontinued than in the other two groups (5 vs 2 vs 2). However, 2 of these discontinuations were subjects who were enrolled and were subsequently found to be ineligible and were, therefore, not vaccinated.*

Protocol Deviations

- There were a total of 38 protocol deviations in the study. Twenty-six were due to study visits outside the window period. The remaining reasons included missing study visits, arm check, or signing forms. Deviations were considered minor and were not felt to significantly impact the results of the study. Seven subjects were excluded from the Evaluable Populations as noted in Table 8.1.4-4 above because they received TIV, were pregnant, or did not have a 28 day HAI titer.

Demographics and Baseline Characteristics

- Demographics and baseline characteristics for study PSC01 participants are presented in Table 47.

Table 47 Demographics and Baseline Characteristics – PSC01

Characteristic	Flublok 75µg n=151 (%)	Flublok 135µg n=153 (%)	Placebo n=154 (%)	U.S. Population July 2007
Race White/Caucasian	126 (83)	130 (85)	139 (90)	81.3%
Race Black/African/American	12 (8)	9 (6)	9 (6)	13.0%
Race Latino/Hispanic*	2 (1)	5 (3)	1 (1)	7.4%
Race Asian	10 (7)	4 (3)	4 (3)	4.5%
Race American Indian/Alaska Native	0	1 (1)	0	1.0%
Race Native Hawaiian/Pacific Islander	1 (1)	1 (1)	0	0.2%
Race Other	0	3 (2)	1 (1)	**
Gender Male	48 (32)	57 (37)	65 (42)	**
Gender Female	103 (68)	96 (63)	89 (58)	**
Age (years) Mean (SD)	32	31.3	31.9	**
Age (years) Median	32	30	32	**
Age (years) Min-Max	18,49	18,49	18,49	**

Source: Table 14.1.3, Module 5, Volume 1, p89, and the electronic datasets

*Hispanic origin is considered an ethnicity, not a race, and Hispanics may be of any race.

**Determined only for race/ethnicity in 2007.

- The mean age of subjects receiving Flublok 135µg was 31 years and the majority of subjects were female (63%). Overall, 85% of subjects were Caucasian, 6% African American, 3% Latino/Hispanic, 3% Asian, and 2% Native American. There were slightly more Caucasians and females in the Placebo group relative to the Flublok groups, and more Asians in the lower dose Flublok group. Overall, baseline demographic characteristics were similar among the three groups.

Past Medical History

Assessment of the past medical history, according to treatment group, of study PSC01 participants was based on review of the electronic datasets (data not shown).

Reviewer comment: No important imbalance in past medical history was noticed among treatment groups. No subjects with autoimmune or immunodeficiency diseases were identified.

Concomitant Medications

The electronic source datasets were evaluated and revealed no subjects who were taking immunosuppressive doses of medications.

8.1.4.2.2 Efficacy/Immunogenicity Endpoints

Primary Immunogenicity Endpoint: Seroconversion to a minimum HAI titer 1:8

- The proportion of subjects in each treatment group who demonstrated a 4-fold rise in HAI titer at Day 28 is presented in Table 48. The pre-specified criterion was a 4-fold increase from pre-vaccination titer to a minimum Day 28 titer of 1:8. The difference in proportions between the two Flublok dose groups as well as the p-value is also presented:

**Table 48 Percentage 4-fold Rise in HAI Titer to $\geq 1:8$ at Day 28 -
Evaluable Population – PSC01**

Strain	Parameter	Flublok 75 μ g n=150	Flublok 135 μ g n=150	Placebo n=151
H1N1	% 4-fold rise	51	67	3
H1N1	LB 95% CI	42.4	59.2	--
H1N1	Difference 75 v 135 μ g*	-0.167	-0.167	--
H1N1	p-value**	0.005	0.005	--
H3N2	% 4-fold rise	81	77	11
H3N2	LB 95% CI	73.4	69.1	--
H3N2	Difference 75 v 135 μ g*	0.040	0.040	--
H3N2	p-value**	0.481	0.481	--
B strain	% 4-fold rise	65	92	4
B strain	LB 95% CI	57.1	86.4	--
B strain	Difference 75 v 135 μ g*	-0.267	-0.267	--
B strain	p-value**	<0.001	<0.001	--

Source: Table 14.2.3.1, Module 5, Volume 1, pp108-110

*Difference in the proportions between the Flublok 75 μ g and 135 μ g treatment groups.

**p-value for the difference in the proportions between the Flublok 75 μ g and 135 μ g treatment groups.

“--” not calculated for placebo group

Reviewer comment: Both the Flublok 75 μ g and 135 μ g dose groups met the pre-specified criteria for seroconversion for all three strains. However, the criteria used are not those specified in the CBER guidance document of May 2007. There was a significant difference between the proportion of subjects responding to the 15 μ g of H1 and B antigens in the low dose group as compared to the 45 μ g of H1 and B antigens in the high dose group (51% versus 68% and 65% versus 92% respectively). The difference in responses to H3 between the two Flublok treatment groups were not significantly different, $p=0.481$, as expected since both study vaccines contained 45 μ g of HAI antigen. Subjects in the placebo group did not mount a significant immune response to the study vaccine by these criteria.

Exploratory or Post Hoc Immunogenicity Endpoints

- Seroconversion was also analyzed post hoc using modified CBER criteria where, for each strain, the proportion of subjects in the Flublok group who seroconverted by Day 28 was defined as those with a post-vaccination HAI titer of $\geq 1:64$ in subjects with a pre-vaccination HAI titer of $<1:4$ (LOD for HAI assay was a titer of 1:4; undetectable or negative titers were assigned a value of 1:2 in this study), or a ≥ 4 -fold rise in HAI titer on Day 28 in subjects with a prevaccination titer of $\geq 1:4$, to a minimum Day 28 titer of 1:64. The lower bound of the 2-sided 95% CI should meet or exceed 40%. A similar analysis was performed with a less conservative HAI cutoff titer of 1:32.
- For each strain, the proportion of subjects in the Flublok group who achieved a post-vaccination HAI titer of $\geq 1:64$. The lower bound of the 2-sided 95% CI

should meet or exceed 70%. A similar analysis was performed with a less conservative HAI cutoff of 1:32.

Reviewer comment: *For purposes of the review, the reviewer will present results only for the more stringent criteria of HAI titer $\geq 1:64$ and not the HAI cutoff of 1:32 which, although it represents a 16-fold rise from a negative titer of 1:2, is lower than the CBER cutoff of 1:40.*

- Immunogenicity results based on post-hoc analyses are presented in Table 49.

Table 49 Immunogenicity Results Based on Post-Hoc Analyses (Modified CBER Criteria)
PSC01 Evaluable Population: post-vaccination titer cut-off = 1:64

Strain	Parameter	Flublok 75mcg N=150 n(%)	Flublok 135mcg N=150 n(%)	Placebo N=151 n(%)
H3	% seroconversion	41	60	0
H3	LB 95% CI	32.7	51.7	0
H3	Meets acceptance criterion?	NO	yes	NO
H3	% Day 28 HAI titer $\geq 1:64$	77	87	40
H3	LB 95% CI	70	80.9	32.5
H3	Meets acceptance criterion?	Yes	Yes	NO
H1	% seroconversion	80	77	9
H1	LB 95% CI	72.7	69.1	5.2
H1	Meets acceptance criterion?	Yes	Yes	NO
H1	% Day 28 HAI titer $\geq 1:64$	99	100	66
H1	LB 95% CI	96.3	97.6	57.4
H1	Meets acceptance criterion?	Yes	Yes	NO
B	% seroconversion	31	63	1
B	LB 95% CI	24.0	55.1	0
B	Meets acceptance criterion?	NO	Yes	NO
B	% Day 28 HAI titer $\geq 1:64$	39	65	7
B	LB 95% CI	31.5	57.1	3.2
B	Meets acceptance criterion?	NO	NO	NO

Source: Tables 14.2.4.1 and 14.2.1.1, Module 5, Volume 1, pp114 and 93

- In the Exploratory, post hoc analyses, Flublok 135 μ g exceeded 5 of the 6 modified immune response criteria. The proportion with post-vaccination HAI titer $\geq 1:64$ failed criteria for the B strain. Flublok at the 75 μ g dose failed 3 of 6 criteria: seroconversion for the H1N1 and B strains and proportion HAI $\geq 1:64$ for the B strain. The placebo group did not demonstrate an immune response by the modified criteria.

Reviewer comment: *For the B antigen, a greater proportion of subject who received the 45 μ g dose met the modified acceptance criteria than did those who received the 15 μ g dose, supporting the selection of the 135 μ g total dose of Flublok for licensure. Differences between the ability of the two dose levels to meet the exploratory endpoints were not as apparent for the H1 and H3 antigens. Perhaps this was related to the higher threshold set for the exploratory endpoints (4-fold rise to a minimum of 1:64 versus 1:8).*

- The Applicant also analyzed GMTs among the treatment groups to further explore differences in immunogenicity (Table 50).

Table 50 Geometric Mean Titer and 95% Confidence Interval – Evaluable Population – PSC01

Day	Dose Group	H1 GMT (95% CI)	H3 GMT (95% CI)	B GMT 95% CI
Day 0	Placebo (N=151)	26.4 (19.9, 35.0)	72.8 (56.4, 93.9)	6.1 (5.1, 7.3)
Day 0	Flublok 75µg (N=150)	23.9 (18.0, 31.7)	65.5 (50.7, 84.6)	6.4 (5.4, 7.6)
Day 0	Flublok 135µg (N=150)	22.0 (16.6, 29.2)	74.2 (57.5, 95.8)	5.5 (4.6, 6.5)
Day 28	Placebo (N=151)	28.8 (22.8, 36.4)	68.9 (57.9, 81.9)	5.7 (4.7, 6.9)
Day 28	Flublok 75µg (N=150)	115.6 (91.5, 146.2)	933.6 (784.4, 1111.2)	33.4 (27.6, 40.4)
Day 28	Flublok 135µg (N=150)	206.0 (163.0, 260.5)	1028.7 (864.3, 1224.5)	74.9 (61.9, 90.6)
Day 180	Placebo (N=151)	22.1 (17.3, 28.3)	88.9 (75.1, 105.1)	4.9 (4.0, 6.0)
Day 180	Flublok 75µg (N=150)	57.7 (45.0, 74.0)	587.0 (495.3, 695.8)	15.9 (12.9, 19.7)
Day 180	Flublok 135µg (N=150)	89.5 (69.8, 114.6)	699.3 (590.6, 827.8)	26.9 (21.9, 33.2)

Source: Table 14.2.2.1, Module 5, Volume 1, p103

- For each strain, GMTs at Day 0 were similar among the treatment groups. At Day 28, GMTs in the Flublok 75µg group increased approximately 5- to 14-fold against each vaccine strain whereas GMTs in the 135µg group increased approximately 9- to 14-fold. The 135µg dose elicited higher immune responses to all three strains, particularly for the H1 and B strains. GMTs at Day 28 were much lower for the B strain (74.9) than for H1 (206.0) or H3 (1028.7), but the fold-rise for the B strain indicated a robust response: H1 = 9.4-fold rise; H3 = 13.9-fold rise; B strain = 13.6-fold rise).
- By Day 180, GMTs fell by roughly 50% in both Flublok treatment groups, but remained $\geq 1:40$ to H1 and H3 (89.5 and 699.3 respectively) in the 135µg dose group.

Reviewer comment: *The difference between dose levels for the rise in GMTs for H3 was not as great as for the H1 and B strain antigens most likely because both dose levels contained 45µg of H3 antigen.*

Clinical Efficacy Endpoints:

Assessment of FluBlock clinical efficacy endpoints are presented in Table 51.

Table 51 Clinical Efficacy Endpoints - Evaluable Population - PSC01

Parameter	Flublok 75µg N=150	Flublok 135µg N=151	Placebo N=153	Flublok Overall N=301
Total no. subjects from whom NP swabs were obtained (flu symptom score ≥ 2)	39 (26)	34 (23)	43 (28)	73 (24)
Total # of isolates	4 (2.7)	1 (0.7)	8 (5.2)	5 (1.7)
# of H3N2 isolates	4	0	6	4
# of H1N1 isolates	0	0	0	0
# of B isolates	0	1	2	1
Subjects with culture-positive CDC-ILI (primary efficacy endpoint)	2 (1)	0	7 (5)	2 (1)
-Protective Efficacy (%)	70.9	100.0	nd	85.5
-(95% CI)*	(-53.1, 97.0)	(29.7, 100)	nd	(23.7, 98.5)
-Relative risk [95% CI] placebo vs. vaccine	29.1 (3.0, 153.1)	Nd	nd	14.52 (1.5, 76.3)
Subjects with culture-confirmed symptomatic illness, regardless of whether the subject met the case definition for CDC-ILI, n(%)	4 (3)	1 (1)	8 (5)	5 (2)
Protective Efficacy (%)	49.0	87.3	nd	68.2
(95% CI)*	(-90.4, 88.8)	(5.5, 99.7)	nd	(-10.1, 91.8)
Relative risk (95% CI) placebo vs. vaccine	51.0 (15.7, 165.8)	12.7 (0.2, 94.4)	nd	31.8 (0.08, 110.1)

nd=not determined

* Determined under the assumption of Poisson event rates, according to N.E. Breslow and N.E. Day: *Statistical Methods in Cancer Research*, Volume 2. The Design and Analysis of Cohort Studies. 1987. International Agency for Research on Cancer.)

Data Source: Tables 14.2.5 and 14.2.6.1; Listing 16.2.6.1.

- Overall, there were 2 (1%) cases of culture-confirmed CDC-ILI among Flublok recipients versus 7 (5%) cases in the placebo group. The overall VE for Flublok was 85.5% (95% CI 23.7, 98.5). The VE for Flublok 75µg was 70.9% (95% CI - 53.1, 97.0) and for Flublok 135µg 100% (95% CI 29.7, 100).
- Table 51 also presents the VE of Flublok against culture-confirmed illness regardless of whether the subject met the case definition for CDC-ILI, a post-hoc analysis. VE for Flublok was 68.2% (95% CI -10.1, 91.8) overall, 49.0% (95% CI -90.4, 88.8) for Flublok 75µg and 87.3% (95% CI 5.5, 99.7) for Flublok 135µg respectively.

Reviewer comment: *Thirteen of 451 (2.9%) evaluable subjects had positive nasopharyngeal swabs for influenza. The majority of positive subjects were placebo recipients, and the majority of isolates (10 of 13) were H3N2, Type A/California-like, a drifted variant of the vaccine strain. The attack rate in the placebo group was 5.2%. Although it is difficult to draw firm conclusions about clinical efficacy because the number of cases of culture-confirmed influenza was small, the 75µg dose of Flublok had the same amount of H3 antigen as the 135µg dose, i.e., 45µg. One would, therefore, have expected a similar reduction in cases of influenza A/California-like*

infection in both Flublok treatment groups. The case split for A/California-like influenza, Flublok overall to placebo, therefore, was 4 cases per 301 Flublok recipients versus 6 cases per 153 placebo recipients. There were no matched strains in subjects who developed culture-confirmed influenza. VE of the 135 µg dose was 87.3% (LB 5.5%) against all culture-positive ILI and against all strains regardless of match. Because H3N2 predominated and because both the 75 and 135µg dose groups contained 45µg of H3 antigen, if all cases from subjects who received the 75µg dose are included in the analysis, VE decreased to 68.2% (LB -10.1%). Although the estimates of VE in study PSC01 suggest a favorable trend for both dose levels tested, this study was not powered to test a formal null hypothesis of VE, and it is limited by the overall small sample size and wide confidence intervals.

Immunogenicity and Efficacy Conclusions PSC01

- The 135µg dose of Flublok elicited a higher immune response than the 75µg dose and was selected as the dose to bring forward for further clinical development.
- The primary pre-specified immunogenicity endpoint in this study was the proportion of subjects in each treatment group that demonstrated a 4-fold rise in HAI titer at Day 28 to a minimum titer of 1:8. Because FDA guidance criteria for immune response is based on a different dilution series than the one used in this study, seroconversion was analyzed in a post hoc analysis using criteria modified from FDA Guidance with a minimum Day 28 HAI titer of 1:64 rather than 1:40. Vaccination with a single dose of Flublok 135µg elicited an immune response that exceeded 5 of the 6 modified immune response criteria. The B strain did not meet criteria for the proportion of subjects with a post-vaccination HAI titer $\geq 1:64$ (lower bound of the 2-sided 95% CI = 57.1% rather than 70%). However, if the post-vaccination threshold was changed to an HAI titer of $\geq 1:32$, 76.4% (LB) of subjects met the endpoint.
- Flublok at the lower dose of 75µg failed 3 of the 6 modified CBER criteria for immune response: seroconversion for the H1N1 and B strains, and proportion HAI $\geq 1:64$ for the B strain. The low dose formulation contained less antigen (15µg each) for these H1N1 and B strains. The 45µg dose per antigen contained in the 135µg formulation elicited higher immune responses than did the 15µg doses of H1 and B, and supports the selection of the 135µg total dose of Flublok for licensure. Differences between dose levels in immune responses to the H3 antigen were not as great as for H1 and B antigens most likely because both dose levels contained 45µg of H3.
- Flublok 75 µg and Flublok 135 µg demonstrated increases in GMTs at Day 28 ranging from 5- to 14-fold and from 9- to 14-fold respectively. The 13.6-fold rise in GMT for the B strain was robust and comparable to H1 and H3. GMTs to all three vaccine strains fell by roughly 50% by Day 180, but remained $\geq 1:40$ to H1 and H3 in the 135µg dose group.
- Thirteen of 451 (2.9%) evaluable subjects had positive nasopharyngeal swabs for influenza, with an attack rate of 5.2% in the placebo group. The predominant strain (10 of 13 isolates) was H3N2 A/California/7/04-like, a drifted variant from the A/Wyoming/3/03 represented in the vaccine. VE of the 135 µg dose was 87.3% (LB 5.5%) against all culture-positive ILI and against all strains regardless

of match. Because H3N2 predominated and because both the 75 and 135µg dose groups contained 45µg of H3 antigen, if all cases from subjects who received the 75µg dose are included in the analysis, VE decreased to 68.2% (LB -10.1%). The estimates of VE in study PSC01 suggest a favorable trend. However, this study was not powered to test a formal null hypothesis of VE and it is limited by the overall small sample size and wide confidence intervals.

- Although the immunogenicity data are limited by the exploratory nature of the post-hoc analyses, overall the data suggest that Flublok 135µg is immunogenic and suggest a trend towards efficacy in the prevention of influenza.

8.1.4.2.3 Safety Outcomes

- The Safety Population was comprised of all 458 subjects who received a single injection of Study Vaccine including 151 Flublok 75µg recipients, 153 Flublok 135µg recipients, and 154 placebo recipients.
- Summary statistics consisting of frequency counts and percentages were used to report reactogenicity events. Treatment-emergent adverse events (Unsolicited AEs) were tabulated and categorized by SOC and PT. The chi-square test was used to detect significant differences.
- Subjects with missing data were not imputed and were excluded from the denominator when calculating the percentage of subjects with specific AEs. Any event with missing severity data was assumed to be severe, and any event with missing causality data was assumed to be related to the vaccine.
- The safety review was conducted from the source data, the Applicant's tables and line listings, and the electronic datasets, and was descriptive in nature.

Deaths and Serious Adverse Events

- No subject died during the study.
- There were 2 SAEs reported, both of which occurred in the Flublok 135 µg group:
 - Subject #3655(0655), Flublok 135µg, had breast cancer and syncope.
 - Subject #3612(0612), Flublok 135µg, had convulsions.

Neither event was considered related to the vaccine. Narrative summaries of these events, the electronic datasets, and CRFs were reviewed.

Reviewer comment: Neither of these SAEs appeared to be related to Flublok.

Discontinuations Due to Adverse Events

- No subjects discontinued due to AEs. This was confirmed by the electronic datasets.

Unsolicited Adverse Events (Treatment-emergent) According to Severity and Vaccine Relatedness

- The Applicant did not present a summary table of all Unsolicited AEs according to severity in the text of the CSR but did present a table summarizing AEs that were considered possibly, probably or definitely treatment-related through Day

180. The Applicant stated in the text that no treatment-related SAEs or severe AEs were reported. The reviewer assessed all AEs according to severity and vaccine-relatedness based on the Applicants' appendices and the electronic datasets. Twenty-seven percent to 30% of all AEs were assessed as treatment-related. The majority were considered mild in intensity and there were no imbalances among treatment groups (data not shown). Table 52 presents the reviewer's summary of all Unsolicited AEs, SAEs, and Deaths according to severity grade found in the Applicant's submission.

Table 52 Reviewer's Summary of Unsolicited AEs According to Severity and Treatment Group – Safety Population - PSC01

Category	Grade	Placebo N=154		Flublok 75µg N=151		Flublok 135µg N=153	
#subjects with ≥1 AE* n(%), E	n/a	n	E	N	E	n	E
All AEs**n(%), E	Mild	44 (28)	82	48 (32)	70	41 (27)	56
All AEs**n(%), E	Mod	24 (16)	30	16 (11)	24	18 (12)	32
All AEs**n(%), E	Severe	0		1 (0.6)	1	2 (1)	2
All AEs**n(%), E	Life- threatening	0		0	0	0	0
SAEs §	n/a	0	0	0	0	2 (1)	3
Deaths	n/a	0	0	0	0	0	0

Source: Tables 14.3.1.2 and 14.3.1.3, Module 5, Volume 1, pp134-149 and 150-169 respectively, and on the electronic datasets

*subject counted only once regardless of number of events

**AEs regardless of causality. n=number of subjects with AEs. E=number of events. Subjects with multiple AEs in the same body system were counted once per SOC and once per PT using the event with the strongest relationship to the study vaccine.

§includes all SAEs regardless of causality through the end of the study

Reviewer comment: Differences between the reviewer's findings in the electronic datasets and the Applicant's report were small and were not likely to significantly change the interpretation of the overall safety results.

Severe AEs

- No subjects in the placebo arm experienced a severe AE. Three subjects on the Flublok arm experienced one AE each: an infected vaginal mole, a convulsion and a right knee injury.

Definitely related AEs: Two AEs were considered to be definitely related to the study vaccine among all vaccinated subjects. Both were cases of injection site hemorrhage.

Reviewer comment: Among all three treatment groups, most AEs were mild or moderate in severity. No serious or severe AEs appeared related to Flublok.

Events that Occurred in Fewer than 0.5% of Subjects but of Potential Interest

Although individual AEs were reported at low frequency, the datasets were examined more closely for safety signals, in particular for autoimmune or hypersensitivity phenomena, and for idiosyncratic reactions that have been reported following

immunization with a variety of vaccines. A search of the datasets for nervous system disorders, immune system disorders, and musculoskeletal and connective tissue disorders revealed only infrequent reports and no imbalance between study arms.

- **Immune System Disorders:** The datasets were searched for immune system disorders including hypersensitivity, rash, allergic reaction, and revealed only one case of drug hypersensitivity (allergic reaction to neomycin). In addition, the Applicant was asked to provide narratives and CRFs for any subject who experienced these types of AEs. No other cases were reported.

Reviewer comment: The clinical reviewer concurred that the case of neomycin hypersensitivity was unrelated to receipt of Flublok.

- **Rash:** Rash occurred in two subjects, both in the Flublok 75µg group. Subject 2401 experienced rash in the left axillary area 22 days post-vaccination. Subject 2441 experienced a rash in the left antecubital area 4 days post-vaccination. Neither was considered serious, both were assessed as mild and unrelated to the study vaccine, and both resolved without sequelae.
- **Oculorespiratory Syndrome:** There were no cases suggestive of ORS.

Unsolicited Adverse Events Occurring in $\geq 0.5\%$ of Subjects Regardless of Causality

The Applicant's report and the electronic datasets were evaluated for all Unsolicited AEs regardless of vaccine relatedness that occurred from Day 0 through Day 180 in at least 0.5% of subjects according to MedDRA SOC and PT.

- The most frequently reported AEs in the Flublok 135µg group were: headache (7.8%), URI (5.9%), pharyngolaryngeal pain (4.6%), and cough (3.9%).
- The most frequently reported AEs in the Flublok 75µg group were: headache (6.0%), pharyngolaryngeal pain (4.6%), cough (4.0%), and URI (3.3%).
- The most frequently reported AEs in the Placebo group were: headache (8.4%), pharyngolaryngeal pain (5.2%), URI (4.5%), nasal congestion (4.0%), and myalgia (3.2%).
- Among all Flublok recipients, there were more cases of nausea (1.6% vs 0), sinusitis (1.6% vs 0.6%), and cough (4.0% vs 1.9%) than in the placebo group.

Reviewer comment: Overall, the frequencies of Unsolicited AEs were low. There were no important imbalances among the three treatment groups, and no unusual patterns or trends were observed. Results derived from evaluation of the electronic datasets were identical to those reported by the Applicant.

Review of Unsolicited Adverse Events and Relationship to Study Vaccine

All Unsolicited AEs that were considered to be related or possibly related to the study vaccines according to SOC and PT were reviewed.

- A total of 57 subjects (12%) had Unsolicited AEs assessed as either possibly, probably or definitely related to the study vaccines: 21 (14%) in the Flublok 75µg group, 16 (10%) in the Flublok 135µg group, and 20 (13%) in the placebo group.

- Overall, the most frequently reported treatment-related AEs by treatment group were:
 - Flublok 75µg: pharyngolaryngeal pain (3%), cough (2%), headache (2%), and URI (2%).
 - Flublok 135µg: headache (2%) and pharyngolaryngeal pain (2%).
 - Placebo: nasal congestion (3%)

Reviewer comment: There were no important imbalances or trends among the treatment groups in AEs assessed as treatment-related.

8-Day Solicited Reactogenicity Events (Day 0-Day 7)

The summary of reactogenicity events was based on review of the Applicant's Tables 14.3.6.2 and 14.3.6.5, Module 5, Volume 1, pp256-259 and 282, derived from review of the subjects' diary cards. Assessments were also performed by the investigators on Days 2 and 8. Because the investigators recorded fewer events, the more conservative diary card data was used for purposes of the review.

- Most reactions were considered mild or moderate. There were three severe events reported: one case of soft swelling, one case of fatigue, and one case of sweating all three in the Flublok 135µg group.
- The majority of subjects reported no local injection site reactions. Local pain was the most frequently reported reaction, and this occurred predominantly in Flublok recipients: placebo 17%, Flublok 75µg 44%, and Flublok 135µg 61%. The majority of pain was described as mild (Grade 1). Other local reactogenicity events occurred at low frequencies and without marked differences among treatment groups.
- Systemic symptoms were reported by more Flublok recipients overall: placebo 64%, Flublok 75µg 73% and Flublok 135 µg 80%. The majority of reactions were mild in severity. Most frequent were: headache (placebo 41%, Flublok 75µg 35% and Flublok 135 µg 43%); tiredness/lack of energy (placebo 33%, Flublok 75µg 30% and Flublok 135 µg 26%); fatigue (placebo 19%, Flublok 75µg 19% and Flublok 135 µg 16%); and muscle pain (placebo 12%, Flublok 75µg 17% and Flublok 135 µg 20%).
- Subject diary cards documented only 2 subjects with fever within 8 days of vaccination. Both subjects received Placebo and reported Grade 1 fever, <100.4°F.
- According to the subjects' diary cards, there were few residual symptoms by post-vaccination Day 7, primarily tiredness/lack of energy (n=22) and headache (n=22), approximately equal numbers among the treatment groups. There were only 2 subjects with mild residual bruising at the injection site by Day 7, both in the Flublok 135µg group.

Reviewer comment: Other than local pain which was reported by more recipients in the Flublok groups, there were no large or important differences in solicited symptoms among the treatment groups. No safety concerns were raised.

Pregnancies

There were a total of 3 pregnancies during the study through Day 180. All three pregnancies occurred in Flublok recipients:

- Subject #0476, Flublok 75µg, was reported by the Applicant as having had a positive pregnancy test at the time of randomization, and was 5 weeks pregnant at the time of vaccination. She is reported as having normal prenatal tests and as having a normal term delivery.
- Subject #0380, Flublok 75µg, a 19 year old female who was on an oral contraceptive and whose pregnancy test was negative at the time of vaccination, became pregnant approximately 3 months after vaccination. She had an elective termination at approximately 12 weeks gestation.
- Subject #0152, Flublok 75µg, became pregnant approximately 20 weeks after vaccination and had an elective termination at approximately 8 weeks gestation. The products of conception were not examined.

Case Reports Reviewed for Study PSC01

CRFs were reviewed for the SAEs reported in subjects #0655 (breast cancer and syncope) and #0612 (hypoglycemia and convulsions).

Vital Signs

There were no unexpected treatment emergent trends or patterns in vital signs identified following Flublok administration in study PSC06.

Laboratory Evaluation

There were no routine clinical laboratories performed for the study other than screening urine pregnancy tests.

8.1.4.3 Comments Study PSC01: Safety and Efficacy Conclusions

Overall, the safety and immunogenicity data supported further clinical development of the 135µg dose of Flublok. The data suggest that, for the H1N1 and B strains, Flublok 45µg per antigen is more immunogenic and successful in meeting immune response criteria than is the 15µg dose. Because of the small sample size, vaccine efficacy data were not sufficient to draw firm conclusions, but do suggest a favorable trend.

8.1.5 Trial #5 - PSC02

“Evaluation of the Safety, Reactogenicity and Immunogenicity of Flublok Trivalent Recombinant Baculovirus-Expressed Hemagglutinin Influenza Vaccine Administered Intramuscularly to Healthy Children Aged 6 to 59 Months”.

- A narrative summary and synopsis of this trial were submitted to the BLA as supportive information regarding the pediatric development plan. Source data were not submitted for review.
- PSC02 was a Phase 1/2, randomized, double-blind, active-controlled, multi-center dose-finding trial of Flublok in healthy pediatric subjects aged 6 to 59 months conducted in the 2006-2007 influenza season. The purpose of the study was to evaluate the safety, reactogenicity and immunogenicity, and to determine

the optimal dose and dosing regimen of Flublok as compared to Fluzone in two age groups: children aged 6 to 35 months and 36 to 59 months.

- A total of 156 subjects were enrolled (planned n=300). The 6-35 month old group (n=115) was randomized 1:1:1 to receive two 135µg doses of Flublok, two half-doses (67.5µg per dose) of Flublok, or two half-doses of Fluzone (22.5µg HA per dose). The 35-59 month old group was randomized 1:1 to receive either two 135µg doses of Flublok or two 45µg doses of Fluzone.
- The Applicant reports that the vaccines were well-tolerated and that no SAEs occurred with either vaccine. No apparent differences in AEs were noted between the Flublok and TIV groups.
- The Applicant reports that SCRs to the H1 strain were significantly lower in the Flublok groups than for Fluzone among subjects 6-35 months (43% in the low dose Flublok group, 56% in the high dose Flublok group, and 94% in the Fluzone group). In the 36-59 month old groups, SCRs to H1 were similar for Flublok (94%) and TIV (95%). SCRs to the H3 strain were also significantly lower in the Flublok groups as compared to Fluzone in the 6-35 month old age groups (33% for both low and high dose Flublok groups and 75% for the Fluzone group). In the 36-59 month old group, the SCR to H3 for Flublok was 75% vs 89% for Fluzone.
- The Applicant states that these low immune responses for Flublok were more pronounced in subjects who were seronegative at baseline, suggesting that Flublok is less immunogenic than Fluzone in young children.
- In the April 2009 CR, the Applicant reported that interpretation of the immunogenicity results for the B strain was confounded by the fact that the B strain represented in Flublok was B/Ohio/01/05 whereas the B strain represented in Fluzone was B/Malaysia/2506/04. Therefore, immunogenicity results were not reported for the B strain in the April 2009 CR.
- The Applicant concluded that Flublok is less immunogenic than TIV in these pediatric age groups, especially in seronegative subjects, and that further dose escalation studies with and without alum adjuvant would be required to determine an appropriate formulation of Flublok in children.

Reviewer comment: In response to FDA Information Requests for more detailed and definitive Pediatric Plans, the Applicant submitted amendments STN 125285/0.18, 0.60, and 0.61. Included were additional immune response data, including responses to the B strain, suggesting that both younger age and baseline seronegative status within age subgroups were associated with low immune responses. Responses to the B strain were lower than to H1 and H3. As the reviewer commented in study PSC03, the antigens Flublok B/Ohio/01/05 and Fluzone B/Malaysia/2506/04 were considered antigenically equivalent by the WHO so that immune responses to the vaccines should not have been significantly different on the basis of the different B strains used in each vaccine. Please see the Pediatric Plan in Section 11.3 Special Populations for review of the amendments to the Pediatric Plan.

9.0 Overview of Efficacy Across Trials

9.1 Indication

For active immunization of adults 18 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

9.1.1 Methods

Data from four clinical trials conducted under U.S. IND 11951 were submitted by the Applicant in support of efficacy: PSC01, PSC03, PSC04, and PSC06. PSC01 and PSC04 were placebo-controlled trials that enrolled healthy adults 18 through 49 years of age. PSC03 and PSC06 were active-controlled studies comparing Flublok to TIV (Fluzone) in two older adult populations: medically stable adults 50-64 years of age (PSC06) and medically stable adults ≥ 65 years of age (PSC03). For details of the individual clinical trials, please refer to Section 8, Clinical Studies and see Table 1, Table of Clinical Trials, in Section 6.2.

9.1.2 Efficacy Endpoints

The clinical studies submitted to the BLA assessed humoral immunogenicity by the use of the HAI assay to measure HAI titers. Neutralizing antibody against hemagglutinin is the primary immune defense against infection with influenza. Although there is no validated immune correlate of protection, previous studies suggest that HAI titers of 1:32 to 1:40 correlate with protection against illness. The FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines: May 2007, has indicated that for the purposes of accelerated approval of trivalent inactivated influenza vaccines, the HAI antibody response may be an acceptable surrogate marker of activity that is reasonably likely to predict clinical benefit. (See Section 8.0 for the 2007 Guidance on immunogenicity criteria for effectiveness.)

For studies PSC01, PSC04 and PSC06, the primary endpoints utilized the HAI assay to measure immune response according to the aforementioned FDA guidance criteria. For PSC03 and PSC06, the HAI assay was also used to calculate SCRs and GMT ratios to assess non-inferiority of Flublok versus Fluzone in accordance with the FDA Guidance as follows:

- The UB of the 2-sided 95% CI of the GMT ratio ($\text{GMT}_{\text{US licensed TIV}}/\text{GMT}_{\text{Flublok}}$) 28 days post-vaccination should not exceed 1.5.
- The UB of the 2-sided 95% CI on the difference between the SCRs ($\text{SCR}_{\text{US licensed TIV}} - \text{SCR}_{\text{Flublok}}$) should not exceed 10%.

Studies PSC03, PSC04 and PSC06 performed exploratory analyses to evaluate the impact of pre-vaccination HAI titers and previous influenza vaccination status on immune response. Because these analyses were exploratory and were not powered for statistical significance, the results of these analyses are not provided or discussed for the individual clinical studies in Section 8. To summarize these results, there was a trend suggesting that Flublok is more immunogenic in subjects who have low baseline HAI titers and/or who have not been exposed to vaccine antigen in the previous influenza season. This

trend was more evident in the older age groups. The older age groups also had a greater proportion of subjects with a history of influenza vaccination in the previous influenza season than did their younger counterparts. The fact that more older subjects may have started out with a higher baseline HAI titer by virtue of previous vaccination may partially explain the greater difficulty this age group had in demonstrating a significant 4-fold rise in HAI titer as opposed to achieving a post-vaccination HAI titer $\geq 1:40$. Unlike the adult populations, in the pediatric study PSC02, immune responses were lower in immunologically naïve recipients of Flublok 6-35 months of age. The Applicant postulated that the low immunogenicity might be due to the fact that, in comparison to egg-derived antigens, HA antigens produced in insect cells are less heavily glycosylated and are not cleaved. The Applicant hypothesized that complex glycosylation and cleavage of the HA antigens (egg-derived) may be important in priming immunologically naïve infants. The reviewer is not able to comment on this hypothesis.

All four clinical studies assessed influenza illness as a clinical endpoint of efficacy. The results of the efficacy endpoints for studies PSC04 and PSC06 were not available at the time of the original BLA submission that requested licensure under accelerated approval regulations. These data were submitted with the Complete Response along with a revised request for tradition approval.

The influenza virus HAI assay for all clinical studies conducted under IND 11951 was performed by a single central laboratory: the Laboratory for Specialized Clinical Studies (LSCS) at the CCHMC in Cincinnati, OH. Dr. Lev Sirota reviewed and approved the assay validation in 2007. For further discussion of the HAI assay validation, please see Section 4.4 of this review, the Statistical Assay Review by Dr. Sirota, and relevant sections of the Statistical and CMC reviews.

Viral cultures for the clinical endpoint studies were performed by the -----
------(b)(4)-----

9.1.3 Study Design

A comparison of study design across clinical trials is presented in Table 53:

Table 53 Study Design across Clinical Studies

Study/ Date	Phase	Age	Flublok n*	Flublok n**	Control n	Rdm	Blind	Sites (all US)
PSC01 2004-2005	2	18-49	150	153***	154 Placebo	1:1:1	MDB	3
PSC03 2006-2007	3	≥65	431	436	433 Active	1:1	MDB	6
PSC04 2007-2008	3	18-49	448	2344	2304 Placebo§	1:1	MDB	24
PSC06 2007-2008	3	50-64	299	300	302 Active	1:1	MDB	6
Total # subjects	--	--	1328	3233	3193	--	--	--

*n=evaluable population for immunogenicity

**n=evaluable population for safety and clinical efficacy analyses

***135mcg dose

--“ = not applicable

Rdm=randomization

MDB = modified double-blind where all subjects, site staff and laboratory personnel involved in efficacy evaluations were blinded except for the person administering the vaccine.

§Placebo control for safety and culture-confirmation, but originally no control for immunogenicity subset. Post-hoc immunogenicity subset (n=127) randomly selected.

- All four trials were prospective randomized modified double-blind well-controlled multicenter studies. For studies that performed exploratory analyses evaluating the effect of influenza vaccination in the previous season, stratification and randomization procedures were very similar.

Reviewer comment: One difference between PSC04 and the other studies was that, for the immunogenicity subset, subjects in the placebo group had blood drawn for serologies, but the samples from these subjects were stored and not sent to the central lab for the assays to be run. Thus, a limitation in study design was that PSC04 had a placebo control for safety and for the culture confirmation study, but not for the lot-to-lot consistency/immunogenicity subset. The Applicant responded to the FDA CR letter request to perform a post hoc immunogenicity analysis on a randomly selected subset of subjects from the placebo group. These results were presented in Section 8.1.1.2.2, efficacy outcomes for study PSC04.

- All studies evaluated the trivalent 135µg dose of Flublok intended for licensure containing 45µg each of recombinant hemagglutinin antigen from the H1, H3 and B strains. As previously mentioned, PSC01 also evaluated a 75µg dose of Flublok in an additional 150 subjects as part of the dose-finding study. This formulation contained 15µg H1, 45µg H3 and 15µg B strain HA antigens.
- All studies used the same criteria for obtaining NP or a combination of NP and TS from subjects who had an ILI, “flu symptoms” score of 2 or greater, based on a standardized “flu symptoms card” completed by all subjects throughout the influenza season surveillance period. The surveillance period was defined across studies by very similar criteria using local and CDC laboratory surveillance.
- All studies used the same CDC-ILI case definition of fever (≥100°F) plus either cough or sore throat on the same day or on consecutive days for the pre-specified

primary clinical endpoint, and a broader definition of ILI for secondary/exploratory endpoints.

- Duration of follow-up was the same for the four studies, 28 days for post-vaccination HAI titers, EOIS (at least 6 months) for influenza surveillance and culture confirmation data, and 180 days for safety follow-up.
- Inclusion and exclusion criteria were almost identical, without significant differences, across studies.
- The Phase 2 dose-finding study, PSC01, was adequate to determine the optimal dose to be used in the Phase 3 studies. For further details, please see Clinical Studies, Section 8.

9.1.4 Efficacy findings

Baseline Characteristics across Studies

The baseline characteristics of study participants across studies are presented in Table 54.

Table 54 Baseline Characteristics across Studies

Study	Age Group	n*	Mean Age	M/F %	Prior year Flu vaccine % Flublok	Prior year Flu vaccine % Control
PSC01	18-49	150	31	37/63	n/a	n/a
PSC03	≥65	431	72.9	48/52	83	84
PSC04	18-49	448	32.8	46/54	21	n/a**
PSC06	50-64	299	55.9	38/62	69	70

*n=Evaluable population. In the CSR, the n for age/gender was 422, and the prior year vaccination status was based on the ISR n=391.

**this variable was not evaluated in the the post hoc placebo group analyses

Reviewer comment: *Approximately 32% of the Evaluable Population across studies was 65 years of age or older, providing valuable information regarding this age group most vulnerable to the complications of influenza. There was a greater proportion of female subjects overall, but the male-to-female ratio was closer to 1:1 in the 2 largest studies, PSC04 and PSC03. As expected, the older age groups had a greater proportion of subjects with a history of influenza vaccination in the previous influenza season than did their younger counterparts. The fact that more older subjects may have started out with a higher baseline HAI titer by virtue of previous vaccination may explain in part the greater difficulty in demonstrating a significant 4-fold rise in HAI titer as opposed to a post-vaccination HAI titer $\geq 1:40$ in this age group.*

Race/ethnicity across Trials

Race and ethnicity of subjects across all trials are presented in Table 55.

Table 55 Race/Ethnicity across Trials

Race/ Ethnicity	PSC01 %	PSC03 %	PSC04 %	PSC06 %	US Population July 2007 %
White/Caucasian	85	99	65	70	81.3
Black/African American	6	<1	19	3	13.0
Latino/Hispanic *	3	<1	9	10	7.4
Asian	3	0	5	12	4.5
American Indian/Alaska Native	1	0	<1	<1	1.0
Native Hawaiian/Pacific Islander	1	0	<1	4	0.2
Other	2	<1	1	4	Nd

*Hispanic origin is considered an ethnicity, not a race, and Hispanics may be of any race.

nd=not determined

Reviewer comment: *Individually, none of the studies closely resembled the U.S. population census data from 2007, but representation across studies was reasonably close.*

Reviewer comment: *In the CSR for PSC04, the number of subjects analyzed by the Applicant for subject demographics was n=422 rather than 448. It was not clear why 26 subjects were missing from this analysis. The Applicant's demographic reports using these two different subsets (ISR versus CSR) are almost identical, and do not impact the overall interpretation of the demographic results.*

Past Medical History was similar across studies, and **Concomitant Medications** were equally devoid of significant immunosuppressive medications.

Product Equivalence

Only two TIVs were used across the four studies: Flublok, two dose formulations, and Fluzone (sanofi pasteur).

Flublok was comprised of three full length recombinant HA proteins expressed in *expresSF+* (Lepidopteran) insect cells by a recombinant baculovirus expression vector. Fluzone is a trivalent inactivated split virus manufactured in chicken embryos (hen eggs).

Flublok contains 45µg of HA antigen for each of the three virus strains whereas Fluzone contains 15µg of HA per strain. Both products are thimerosal-free. The vaccine antigen content of the vaccines used in the studies submitted in support of this BLA, according to study and year, can be found in Table 56.

Table 56 Vaccine Antigen Content according to Study and Year

Year	Study	Strain	Flublok (45µg HA/strain)	Fluzone (15µg HA/strain) (or placebo)
2004-2005	PSC01	H1N1	A/New Caledonia/20/99	Placebo
2004-2005	PSC01	H3N2	A/Wyoming/3/03	Placebo
2004-2005	PSC01	B	B/Jiangsu/10/03	Placebo
2006-2007	PSC03	H1N1	A/New Caledonia/20/99	A/New Caledonia/20/99
2006-2007	PSC03	H3N2	A/Wisconsin/67/05	A/Wisconsin/67/2005
2006-2007	PSC03	B	B/Ohio/01/05	B/Malaysia/2506/2004
2007-2008	PSC04	H1N1	A/Solomon Islands/03/2006	Placebo
2007-2008	PSC04	H3N2	A/Wisconsin/67/2005	Placebo
2007-2008	PSC04	B	B/Malaysia/2506/2004	Placebo
2007-2008	PSC06	H1N1	A/Solomon Islands/03/2006	A/Solomon Islands/03/2006
2007-2008	PSC06	H3N2	A/Wisconsin/67/2005	A/Wisconsin/67/2005
2007-2008	PSC06	B	B/Malaysia/2506/2004	B/Malaysia/2506/2004

Bold font indicates difference in vaccine strains between Flublok and Fluzone for a specific year and antigen

Reviewer comment: In studies PSC03 and PSC06, the only studies which utilized a Fluzone active control, the vaccines were comprised of the same influenza virus strains with the exception of the B strain in study PSC03. In PSC03 Flublok B/Ohio/01/05 and Fluzone B/Malaysia/2506/2004 were antigenically related and interchangeable according to WHO recommendations. Therefore, the immune responses to these two strains should have been similar.

Comparison of Immunogenicity Results Across Trials

Table 57 summarizes the immunogenicity results across trials (for PSC01, only the 135µg dose group results are presented).

Table 57 Immune Response and Non-inferiority Endpoint Across Clinical Studies – Flublok 135µg

Strain	Parameter	PSC01 n=150 Age 18-49 2004-2005	PSC04 n=448 Age 18-49 2007-2008	PSC06 n=299 Age 50-64 2007-2008	PSC03 n=431 Age ≥ 65 2006-2007
H1	SCR (LB 95% CI)*	64 (41.1)	78 (73.5)	72 (66.8)	43 (38.7)
H3	SCR (LB 95% CI)*	81 (73.4)	81 (77.1)	61 (55.4)	78 (73.5)
B	SCR (LB 95% CI)*	49 (41.1)	52 (47.0)	41 (35.2)	29 (25.0)
H1	% HAI ≥ 1:40 (LB 95% CI)**	87 (80.9)	99 (97.1)	96 (93.5)	95 (92.1)
H3	% HAI ≥ 1:40 (LB 95% CI)**	100 (97.6)	97 (94.8)	85 (80.8)	97 (94.3)
B	% HAI ≥ 1:40 (LB 95% CI)**	65 (57.1)	96 (94.0)	93 (89.5)	92 (88.6)
H1	SCR difference (UB 95% CI)	n/a	n/a	1.4	-4.4
H3	SCR difference (UB 95% CI)	n/a	n/a	-9.5	-13.9
B	SCR difference (UB 95% CI)	n/a	n/a	8.2	16.1
H1	GMT ratio (UB 95% CI)	n/a	n/a	0.77 (0.90)	0.85 (0.96)
H3	GMT ratio (UB 95% CI)	n/a	n/a	0.58 (0.68)	0.58 (0.67)
B	GMT ratio (UB 95% CI)	n/a	n/a	1.00 (1.14)	1.30 (1.45)

Bold font indicates where the endpoint did not meet HAI immune response or non-inferiority criteria specified in the FDA May 2007 Guidance criteria.

*PSC01 used a modified (post-hoc) definition of SCR as a ≥4-fold increase in HAI titer to a minimum titer of 1:64 on post-vaccination Day 28.

**PSC01 used a threshold of 1:64 for the Proportion with HAI titer ≥1:40

***based on statistical reviewer's adjusted analyses

SCR difference = SCR TIV – SCR Flublok; GMT ratio = GMT TIV / GMT Flublok

n/a = not applicable because these are placebo controls that did not have an immune response to injection.

- The H1 and H3 strains exceeded both immune response criteria in all four studies. The B strain, however, failed to meet one of the two immune response criteria in each of three of the four studies. In particular, the B antigen had difficulty eliciting a 4-fold increase in the older age groups. HAI responses to the B strain did meet criteria in the largest and pivotal study, PSC04, of young healthy adults.
- For the two studies that evaluated non-inferiority endpoints, PSC03 and PSC06, H1 and H3 strains met both guidance criteria for non-inferiority to Fluzone. The B strain also met the GMT ratio criterion in both studies. However, the SCR was too low to meet the criterion for non-inferiority to Fluzone in study PSC03, adults ≥ 65 years of age. Flublok met all six endpoints for non-inferiority to Fluzone in adults 50 to 64 years of age.
- Study PSC01 re-evaluated the data in a post hoc analysis according to the study's pre-specified HAI antibody dilutions, and used the more stringent modified HAI antibody criterion of 1:64 instead of 1:40 to define success.

Reviewer comment: *The administration of Flublok 135µg elicited an immune response that exceeded FDA guidance criteria for the H1 and H3 strains in all four*

studies representing different age groups and populations, and reflecting manufacturing over three influenza seasons.

The B strain failed immune response criteria in three of four studies and failed the non-inferiority comparison to Fluzone in one of two studies, in adults ≥ 65 years of age. In conclusion, while Flublok's immunogenicity against H1 and H3 appears strong, it is more difficult to draw firm conclusions from the immunogenicity data for the B strain. The relatively low immune responses elicited by the B strain have recurred over the three different influenza seasons and despite a higher antigen content than TIV.

A caveat to the immunogenicity conclusions in all age groups is that concerns persist regarding the HAI assay and the interpretation of HAI titers obtained when BEVS-derived antigens are used in the assay. While the immunogenicity results in adults 18-49 years of age are supported by clinical endpoint data, data to support clinical efficacy do not exist for the older age groups. These concerns must be considered in the overall assessment of the immunogenicity results and will be addressed further in the Conclusions of the Overview of Efficacy.

Lot-to-Lot Consistency

A primary immunogenicity endpoint of study PSC04 was the demonstration of lot-to-lot consistency of Flublok for all three strains. Please see Section 8, Clinical Studies for details of this analysis.

- H3 failed to meet the lot consistency endpoints. This was attributed to a lower rHA H3 antigen content with associated lower GMTs to H3 for lots B and C relative to Lot A. Nevertheless, immune response endpoints by lot for H3 in study PSC04 were met despite H3 lots B and C having less than 45 μ g of HA antigen, and exploratory analyses of clinical efficacy by lot against H3N2 demonstrated similar protection.
- The B strain missed the lower bound of the 95% CI for one comparison, Lot A vs. Lot C, by only a small margin. Please see study PSC04 for details.
- After study PSC04 was conducted, FDA worked with PSC to revise formulation specifications to ensure equal amounts of the HA antigens in the final trivalent vaccine.

Clinical Efficacy

Clinical endpoint data was collected from all four studies submitted to the BLA. Table 57 summarizes Flublok efficacy results against culture-confirmed influenza in the placebo-controlled trials, PSC04 and PSC01.

Table 57 Efficacy of Flublok against Culture-Confirmed Influenza – Placebo-controlled Trials

PSC04 (2007-2008)/ Antigenic match	Isolates or Endpoint	Flublok n=2344 #cases (%)	Placebo N=2304 #cases (%)	%Efficacy	(95% CI)
Matched	-all strains	2 (0.08)	6 (0.26)	n/a	n/a
Matched	-A/H1N1	0	0	n/a	n/a
Matched	-A/H3N2	2 (0.08)	6 (0.26)	n/a	n/a
Matched	-B	0	0	n/a	n/a
Matched	1° endpoint CDC-ILI	1 (0.04)	4 (0.2)	75.4	(-148, 99.5)
Matched	2° endpoint any ILI	2 (0.1)	6 (0.3)	67.2	(-83.2, 96.8)
All Strains	-all strains	64 (2.7)	114 (4.9)	n/a	n/a
All Strains	-A/H1N1	3	9	n/a	n/a
All Strains	-A/H3N2	33	58	n/a	n/a
All Strains	-A/untyped	5	12	n/a	n/a
All Strains	-B	23	35	n/a	n/a
All Strains	-B untyped	0	1	n/a	n/a
All Strains	CDC-ILI ¹	44 (1.9)	78 (3.4)	44.6	(18.8, 62.6)
All Strains	Any ILI ²	64 (2.7)	114 (4.9)	44.8	(24.4, 60.0)
All Strains	Type A ILI ²	41 (1.7)	79 (3.4)	49.0	(24.7, 65.9)
All Strains	Type B ILI ²	23 (1.0)	36 (1.6)	37.2	(-8.9, 64.5)
PSC01 2004-2005/ Antigenic match	Isolates/Endpoint*	Flublok n=151 #cases (%)	Placebo n=153 #cases (%)	%Efficacy	(95% CI)
Matched	-All strains	0	0	n/a	n/a
All Strains	-All strains	1 (0.7)	8 (5.2)	87.3	(5.5, 99.7)
All Strains	-A/H1N1	0	0	n/a	n/a
All Strains	-A/H3N2 (n=151)	0	6	100	(29.7, 100)
All Strains	-B	1	2	49.3	(-87.3, 99.1)
All Strains	CDC ILI all strains	0	7 (5.0)	100	(29.7, 100)
All Strains	Any ILI all strains	1 (0.7)	8 (5.2)	87.3	(5.5, 99.7)
All Strains	A/H3N2 (n=301)**	4	6	66.1	(-29.8, 92.6)
All Strains	H3N2 CDC ILI**	2 (0.7)	5 (3.3)	79.7	(-24.2, 98.1)
All Strains	Any ILI all strains**	5 (2)	8 (5)	68.2	(-10.1, 91.8)

*Analysis were conducted on the 135µg dose group (n=151) only unless marked as **

**For these parameters, H3N2 results from both dose groups (75µg and 135µg, n=151 + 150 respectively) of Flublok are included because both contained 45µg H3N2.

Bold font highlights rows containing results of endpoint analyses

Italics and bold font highlight a row containing results of an exploratory analysis of all culture-confirmed ILI conducted on both dose groups of Flublok (75µg and 135µg, n=151 + 150 respectively) because H3N2 predominated and both dose groups contained 45µg H3N2.

¹pre-specified exploratory analysis

²post-hoc exploratory analysis

n/a = not applicable

RR=(%Flublok positive - % placebo positive)

VE = (1- RR) x 100

Sources: CR Module 5, Vol 2, Tables 23-24, pp81-85, and Tables 14.2.2.1 and Table 14.2.2.2, pp 262-266. BLA Module 5, Vol. 1, Table 14.2.5, pp124-125, and Table 14.2.6.1, pp126-128. Response to IR Amendment 0.17 Tables 1 and 3, p4-6 (6-19-09).

For both placebo-controlled trials, PSC04 and PSC01, the placebo group attack rate was approximately 5%. The 2007-2008 influenza season (PSC04) was characterized by a predominance of antigenically dissimilar or mismatched circulating strains, predominantly H3N2 and B strain. The circulating B strain differed from the vaccine strain in lineage. Despite this, the overall VE against culture-confirmed illness due to any strain was 44.8% (LB 24.4%). Point estimates against all type A and all type B influenza were 49.0% and 37.2% respectively. VE of the 135µg dose in the smaller dose finding study PSC01 was 87.3% (LB 5.5%) against all strains regardless of match or ILI definition. Because the predominant circulating strain was a drifted H3N2 and because both dose groups contained 45µg H3 antigen, if all cases from subjects who received the 75µg dose are included in the analysis, the VE decreased to 68.2% (LB -10.1%) in PSC01.

Reviewer comment: The best estimate of VE in study PSC04 is limited by virtue of being an exploratory post-hoc analysis. However, the pre-specified exploratory endpoint of VE against culture-confirmed CDC-ILI due to all strains was similar, 44.6% with a LB 95% CI of 18.8%. Regarding PSC01, although the attack rate and estimates of VE suggest a favorable trend, this study was not powered to test a formal null hypothesis of VE and it is limited by the overall small sample size and wide confidence intervals.

PSC06 and PSC03 were active-control trials in older adults, 50-64 years and 65 years and older respectively. PSC06 was characterized by a season of predominantly mismatched H3N2 and B strains. The RR of Flublok to Fluzone against any culture positive illness was -76.2%, (LB: -720%). The RR of Flublok to Fluzone in PSC03 was 50.2 (LB: -446.9).

Reviewer comment: In both studies, the attack rates were too small and the 95% CIs were too wide to draw meaningful conclusions regarding the relative risk or relative efficacy of influenza illness in recipients of Flublok compared to Fluzone among older adults. It has been customary for FDA to ask manufacturers of TIVs whose VE failed to meet a LB of the 95% CI of at least 40% against matched strains to conduct a second clinical endpoint study. A second clinical endpoint study in adults 50 years of age and older will be recommended for Flublok post-marketing (Section 13).

Reviewer comment: Vaccine efficacy is dependent on several factors including age, immunocompetence, antigenic match or mismatch between the vaccine and circulating virus, and the specificity of the endpoint measured. Because variability in attack rates and/or antigenic drift can make assessments of VE over a single season difficult, multiple seasons may provide a more accurate estimate of VE. Estimates of efficacy in healthy adults less than 65 years of age have ranged from 70% to 90% when the vaccine and circulating viruses are well-matched. Studies of serologically-confirmed endpoints have generally demonstrated higher rates of efficacy and effectiveness for

TIV than studies using culture-confirmed endpoints. Studies conducted during seasons where the vaccine and circulating strain are poorly-matched have demonstrated lower efficacy. These estimates are limited by a general lack of randomized placebo-controlled trials. Estimates of VE may vary not only over different seasons due to differences in antigenic match, but also among different geographic areas in the same influenza season due to variations in circulating strains from one location to the next. Low attack rates and small sample sizes may also contribute to unreliable estimates of efficacy.

The best estimates of VE for Flublok are derived from the pre-specified and post hoc exploratory analyses in study PSC04 (2007-2008). The attack rate in the placebo group was 4.9%. Absolute VE against culture-confirmed influenza regardless of antigenic match was 44.6% (LB 18.8%) for CDC ILI, 44.8% (LB 24.4%) for any culture-confirmed ILI, 49.0% (LB 24.7%) for any Type A ILI, and 37.2% (LB -8.9%) for any Type B ILI. The efficacy results for Flublok appear comparable to data reviewed by FDA for some other licensed TIVs.

Gender and Race/Ethnicity Sub-Analyses

Sub-analyses of gender, race and ethnicity were requested on the safety, immunogenicity and VE data from PSC01 and PSC04 in an IR dated September 9, 2012. PSC provided an integrated summary of these analyses to FDA on September 28, 2012.

- Integrated immunogenicity data from PSC01 and PSC04 revealed no significant differences in GMTs, SCRs, or proportions of subjects with post-vaccination HAI titers $\geq 1:40$ between males and females. Similarly, no significant differences in these parameters were noted among different racial or ethnic groups.
- Subgroup analyses of vaccine efficacy were restricted to data from PSC04. Attack rates between males and females in placebo groups were similar, 5.2% vs 4.7%, respectively, as were the rates of influenza in the Flublok group, 2.4% vs 2.9%. For all influenza isolates regardless of antigenic match to vaccine strains, there appeared to be a trend toward greater VE in males as compared to females [53.9% (95% CI 23, 73.2) vs 37.9% (95% CI 6.6, 59.1)]. However, CIs were wide and overlapping, and these differences were interpreted as not significant. Estimates of VE for whites and non-Hispanic groups were similar to the overall study population, [49.7% (95% CI 28.3, 65.1) and 44.1% (95% CI 22.9, 59.7)]. Estimates of VE for other racial and ethnic groups had very wide CIs that included zero and were not meaningful because of the very small numbers of subjects with culture-confirmed influenza in these groups. Similarly, estimates of VE for influenza isolates antigenically matched to vaccine strains and comparisons of VE against matched strains among gender, racial and ethnic sub-groups were not meaningful because of the very small numbers of subjects with matched isolates in these sub-groups. Specifically, there were only 2 influenza isolates that matched the vaccine strains, one from a female and one from a male subject, both white, non-Hispanic.

Reviewer comment: There appeared to be a trend toward greater vaccine efficacy against all influenza isolates in males as compared to females, but this did not reach

statistical significance. Overall, gender, racial, and ethnic subgroup analyses of immunogenicity and vaccine efficacy did not reveal significant differences among subgroups. The analyses are limited by small sample sizes and wide confidence intervals, and must be interpreted with caution.

Limitations of the Immunogenicity and Efficacy Findings

- PSC04 was designed and powered for analyses of vaccine efficacy against antigenically similar strains during the 2007-2008 influenza season. Flublok failed to meet the primary and secondary efficacy endpoints. Conclusions regarding VE are based on data driven by mismatched strains and exploratory analyses, both pre-specified and post hoc.
- Lot-to-lot consistency was not demonstrated for the H3 strain in study PSC04. (See review of this in Section 8.1.1.2 for details.)
- HAI assay: The statistical reviewer found that there was unusual variability of GMT responses and ratios across the studies, within and between lots, both before and after adjusting for HAI assays, baseline HAI titers and lots. This raised concerns about the performance of the assay. However, the statistical reviewer concluded that the GMT variability did not significantly influence the overall immunogenicity conclusions. Nevertheless, there remain concerns about the HAI assay validation as well as the interpretation of HAI titers obtained using BEVS-derived antigens in the assay.
- There was a potential break in the blind at Site 5 in study PSC03 for which FDA requested additional information. BIMO inspection of this site did not identify deficiencies that would preclude approval. Additionally, post hoc immunogenicity analyses found no significant differences between Site 5 and the remaining study sites. Therefore, pooling of the Site 5 data with other sites appeared acceptable.
- A change in the planned randomization scheme at Site 13 in PSC04 resulted in a greater number of subjects in the Flublok group (n=2344) versus the placebo group (n=2044). Because the randomization code was not available when the first group of subjects at the site was waiting for vaccination, the investigator made an independent decision to randomize this group into four equal groups (Lot A, Lot B, Lot C and placebo) rather than the intended two groups Flublok and placebo followed by sub-randomization of the Flublok group into the three lots. This deviation from the protocol should not significantly affect the immunogenicity results because subjects were randomized. BIMO inspection of this site did not reveal deficiencies that would preclude approval.
- In the Interim Study Report, the statistical reviewer discovered a discrepancy in study PSC04 between the number of subjects vaccinated with Flublok, n=480, and Day 28 HAI titers in datasets, n=391. A BIMO inspection of this site did not reveal deficiencies that would preclude approval. Sensitivity analyses revealed that the final results and conclusions presented in the CSR were not significantly different from those presented in the ISR.

9.1.5 Efficacy Conclusions

- Clinical efficacy data were collected from all four studies comprising a total population of 3231 adults 18 years and older. However, only PSC04 (adults 18-49 years of age) was adequately powered for statistical hypothesis testing. In the pivotal study PSC04 of young healthy adults, the overall VE against culture-confirmed illness due to any strain was 44.8% (LB 24.4%) despite antigenic mismatch against the predominant circulating H3N2 and B strains. Point estimates against all type A and all type B influenza were 49.0% (LB 24.7%) and 37.2% (LB -8.9%) respectively. The pre-specified exploratory endpoint of VE against culture-confirmed CDC-ILI due to any strain was 44.6% (LB 18.8%). Because circulating B strains may be mismatched by lineage and, therefore, antigenically more distinct, it is not surprising that Flublok showed greater protection against all type A strains than against all type B strains. Although the attack rate and estimates of VE in study PSC01 of young healthy adults also suggested a trend towards protective efficacy, the overall sample size was small and the 95% CIs were wide. PSC06 and PSC03 were active-control trials in older adults, 50-64 years and 65 years and older, respectively. Mismatched strains predominated, and, in both studies, the number of cases were too small and the 95% CIs were too wide to draw meaningful conclusions regarding the relative efficacy in preventing influenza illness in recipients of Flublok compared to Fluzone among older adults.
- One limitation of the clinical endpoint data is that these studies were designed and PSC04 was powered for analyses of vaccine efficacy against antigenically matched strains. Because of the predominance of antigenically dissimilar strains, our conclusions regarding VE are based on exploratory endpoints and analyses driven by mismatched strains, primarily H3N2.
- Although it is not reasonable to require that a vaccine demonstrate protective efficacy against strains not included in the vaccine, FDA accepts that protection against mismatched strains provides evidence for vaccine efficacy. It is reasonable to conclude that Flublok would be at least as efficacious [VE 44.8% (LB 24.4%)] against antigenically similar virus strains in healthy adults 18 through 49 years of age and that these data support licensure in this age group. In fact, the point estimate for the primary clinical endpoint of prevention of culture-confirmed CDC-ILI due to matched strains in PSC04 was 75.4% and may also represent an encouraging trend. However, the cases of CDC-ILI were few (Flublok = 1, placebo = 4), and CIs on the point estimate were wide and included zero. FDA has reviewed VE data to support licensure of several TIVs, and Flublok's VE data are comparable to TIVs with lower VE against all strains from among these studies (for example, Fluarix 004, FluLaval, and Afluria).
- Nevertheless, despite clinical efficacy against antigenically mismatched strains, we do not know with certainty that Flublok would have met the 95% CI lower bound target of 40% VE if matched strains had been circulating. Therefore, to support effectiveness of Flublok in persons 50 years of age and older, CBER will recommend that another clinical efficacy study be conducted.
- Regarding the immunogenicity data, the administration of Flublok 135µg elicited an immune response that exceeded pre-specified acceptance criteria for the H1

and H3 strains in all four studies representing different age groups and populations, and reflecting manufacturing over three different influenza seasons over a four year period.

- In contrast to the type A strains, the B strain failed to meet one of two immune response endpoints in three different studies, and failed the non-inferiority comparison to Fluzone in one of two studies, PSC03, adults ≥ 65 years of age. However, the B strain did meet both immune response endpoints in the largest study, PSC04, of young healthy adults. While Flublok appears immunogenic against H1 and H3, it is more difficult to draw firm conclusions from the immunogenicity data for the B strain.
- The relevance of these results for clinical practice should consider that influenza type A, in particular H3N2, usually causes more severe disease than type B, results in greater morbidity and mortality in adults, and has circulated in the U.S. for several years. In addition, other licensed traditional egg-grown TIVs (for example, Fluzone, FluLaval, and Afluria) have also shown lower responses to the B strain and have failed to meet immunogenicity endpoints in clinical trials.
- Having drawn these conclusions regarding the immunogenicity data, however, concerns remain regarding HAI assay and the ability to bridge the immunogenicity data to older adult or pediatric populations (see Section 4.4, HAI Assay Validation). Because PSC04 provided adequate vaccine efficacy data to support licensure in persons 18 through 49 years of age, limitations relating to the immunogenicity data are mitigated in this population. However, no clinical endpoint data exist in persons 50 years of age and older to confirm clinical benefit. The reviewer concludes that the efficacy data are not adequate to support full (“traditional”) approval in persons 50 years and older because: 1) the immunogenicity in these older age groups is either low and/or limited by the HAI assay concerns; and 2) the data must be bridged to clinical endpoint data in persons 18 through 49 years of age that are limited by antigenic mismatch and failure to meet the primary clinical endpoint. A second clinical endpoint study conducted in persons 50 years and older may address these concerns by providing data that demonstrate the clinical efficacy of Flublok in older adults.
- In further considering the issues relating to the HAI assay and because PSC04 did not meet the primary clinical endpoint of absolute vaccine efficacy against matched strains, the review team has determined that another clinical endpoint study in the older age groups (50-64 years and 65 years and older) rather than additional immunogenicity data will be needed to support approval in these groups. This is consistent with previous FDA requests to other manufacturers of TIVs to conduct clinical endpoint studies in older or pediatric populations to support licensure.
- The review team has agreed that additional data to support the HAI assay validation and to assess the comparability of BEVS-derived versus egg-derived antigens used in the assay will be needed to facilitate the interpretation of data collected in future immunogenicity studies, including studies to support extension of the age indication to the pediatric population. However, the repeat validation and comparability studies will not be required for the initial approval in persons 18-49 years of age.

- Finally, two differences between Flublok and traditional egg-based TIVs should be mentioned: 1) Flublok required 45µg of HA antigen per strain instead of 15µg per strain to elicit an immune response that met acceptance criteria; and 2) Flublok elicits an immune response only to the recombinant HA antigens in the vaccine whereas the immune response to vaccination with inactivated split-virus antigens includes antibody responses to both HA and neuraminidase (NA). Antibodies to NA restrict release of virus from infected cells and decrease the severity of the infection. However, the primary protective immune response to influenza infection is neutralizing antibody to HA. The studies submitted to the BLA suggest that Flublok elicits responses to HA comparable to TIV. The results of the placebo-controlled trial of clinical efficacy from study PSC04 do not allow a direct comparison of Flublok's vaccine efficacy to currently licensed TIV. The results, therefore, do not allow us to draw conclusions regarding the importance of antibodies to NA to a protective response.

10.0 Overview of Safety Across Trials

10.1 Safety Database – Overall Extent of Exposure

The safety database was obtained from the four studies submitted to the BLA: PSC01, PSC03, PSC04 and PSC06 and is summarized in Table 58. For purposes of the overview of safety review, only subjects who received the 135µg dose intended for licensure will be considered.

Table 58 Overall Extent of Exposure - Flublok

Study	Dose	18-49yr	50-64yr	≥65yr	Mean Age	M/F	Total
PSC01	135µg	153	n/a	n/a	31.3	37/63	153
PSC03	135µg	n/a	n/a	436	72.9	48/52	436
PSC04	135µg	2344	n/a	n/a	32.5	41/59	2344
PSC06	135µg	n/a	300	n/a	55.9	38/62	300
Total ≥18 yr	n/a	n/a	n/a	n/a	n/a	n/a	3233

Source: Table 2.7.4 – 1, Module 2, Volume 1, Section 2.7.4, p4

n/a = not applicable

Demographics

The safety database for Flublok 135µg consisted of 3233 subjects 18 to over 65 years of age. The age and gender of participants are summarized in Table 59 and race/ethnicity composition in Table 60.

Table 59 Age and Gender Characteristics across Studies

Study	Age group	N*	Mean age	M/F, %
PSC01	18-49	153	31.3	37/63
PSC03	≥65	436	72.9	48/52
PSC04	18-49	2344	32.5	41/59
PSC06	50-64	300	55.9	38/62

*n=Safety population

Table 60 Race/Ethnicity across Trials

Race/ Ethnicity	PSC01 %	PSC03 %	PSC04 %	PSC06 %	US Population July 2007 %
White/ Caucasian	85	99	67	73	81.3
Black/ African/ American	6	<1	18	4	13.0
Latino/ Hispanic *	3	<1	11	8	7.4
Asian	3	0	3	12	4.5
American Indian/ Alaska Native	1	0	<1	0	1.0
Native Hawaiian/ Pacific Islander	1	0	<1	<1	0.2
Other	2	<1	1	4	--

*Hispanic origin is considered an ethnicity, not a race, and Hispanics may be of any race. "--" = not available.

- The majority (77%) were young healthy adults 18-49 years of age. Twenty-three percent of subjects were ≥ 50 years of age and 13% were ≥ 65 years of age. Caucasians and females predominated in all studies. Please refer to Section 8, Clinical Studies for discussion of baseline characteristics of individual studies.

10.2 Safety Assessment Methods

Overall, the safety endpoints, methods of collecting data, and statistical analyses were very similar across the four studies allowing a meaningful comparison. The modified double-blind design was used in all studies. The Memory Aids, Flu Symptoms cards, and CRFs were essentially the same. Reactogenicity events were collected through Day 7, Unsolicited AEs through Day 28, SAEs and new onset chronic illnesses through Day 180 in all studies. There were only minor differences in the reactogenicity variables across studies. Toxicity grading scales for solicited and unsolicited events were essentially the same across studies with minor differences in defining the severity grade for fever. Attribution categories also differed only slightly across studies. All AEs were coded according to MedDRA SOC and PT.

All AEs were reviewed by evaluation of the Applicant's summary tables, line listings, narratives, CRFs and electronic datasets. Case narratives, CRFs, and in some instances medical records were requested for all deaths, SAEs, and AEs of special interest such as autoimmune and hypersensitivity events.

There were minor differences in the reactogenicity categories among studies. These differences, however, did not affect the ability to assess reactogenicity across the studies. Toxicity grading scales for solicited and unsolicited events were essentially the same across studies with minor differences in gradations of fever definitions. Causality was defined slightly differently among studies. PSC03 assessed relatedness as "related, unknown or not related", whereas the other three studies assessed relatedness as "definitely related, probably related, possibly related, probably not related and not

related.” These differences, however, did not affect the ability to assess causality across the studies.

10.3 Significant/Potentially Significant Events

10.3.1 Deaths

- There were a total of six deaths across the four studies, 2 occurring in young previously healthy adults (PSC04) and 4 occurring in subjects > 65 years of age (PSC03). The deaths were balanced, 3 in Flublok recipients, 3 in control groups, and none appeared related to the study vaccines.
- There were no deaths reported in studies PSC01 or PSC06 through Day 180. For further details please see Section 8, Clinical Studies

10.3.2 Other Significant/Potentially Significant Events

Serious Adverse Events

SAEs in all four studies were captured through the EOIS visit a minimum of 180 days after vaccination.

Reviewer comment: Of 90 SAEs occurring in 70 subjects in the Flublok group, only 2 events in 2 subjects were considered related or possibly related: pleuropericarditis and vasovagal syncope. There were 90 events in 71 subjects in the control groups, none of which were considered vaccine-related. In PSC04, 7 Flublok recipients (9 events) and 12 placebo recipients (12 events) reported SAEs through Day 28. The highest frequency of SAEs occurred in subjects over 65 years of age, and appeared unrelated to the vaccines. One SAE was found to be important to include in an Adverse Reactions Section 6 of product labeling: the case of pleuropericarditis in PSC04 Subject#05-03221- b(6)--- Please see the detailed case summary of Subject 05-03221- b(6) in Section 8.1.1.2.3 Clinical Studies.

Review of SAEs across studies according to MedDRA System Organ Class revealed that a greater proportion of SAEs were reported from studies that enrolled the elderly population and generally reflected the underlying medical conditions that can be common in an elderly population. Other than vasovagal syncope reported in study PSC06, none of the other SAEs in the elderly population appeared to be attributable to vaccination. There were more infections reported among placebo recipients in study PSC04, but, in general, the types and proportions of SAEs did not differ significantly between Flublok and the control groups.

Severe Unsolicited Adverse Events

Please see the individual study reports in Section 8 Clinical Studies for details of all severe AEs in both treatment groups. There were no severe Unsolicited AEs observed in study PSC01.

Reviewer comment: Across all four studies, there were five severe Unsolicited AEs occurring in three Flublok recipients that were assessed as being related or possibly

related to the study vaccine. When reviewed more closely, only one, injection site swelling, appeared to be related with certainty.

Hypersensitivity or Potential Hypersensitivity Events

Because Flublok is a novel HA antigen manufactured in a novel insect cell culture system, the data was evaluated for hypersensitivity-type events that might be due to residual insect cell proteins in the final Flublok vaccine product. The electronic datasets from each of the four studies (Flublok n=3233) were carefully searched for allergic type reactions using MedDRA PTs that included immune system disorders, hypersensitivity, drug hypersensitivity, adverse drug reaction, allergy, anaphylaxis, hives, urticaria, serum sickness, vasculitis, swelling, angioedema, allergic asthma, anemia, lymphadenopathy, thrombocytopenia, immune thrombocytopenia, arthralgia, myalgia, synovitis, rash, and rash pruritic. The Applicant was asked to provide case narratives, CRFs and consulting physicians' notes for all cases of hypersensitivity-type events. The results of this search are presented below: in Table 61.

Table 61 Potential Hypersensitivity Events Across Studies

Unsolicited AE by MedDRA Preferred Term	Flublok N=3233	Placebo n=2188	Fluzone n=735
Statistic	n (%)	n (%)	n (%)
Pleuropericarditis	1	0	0
Hypersensitivity	4 (0.1)	1 (0.04)	0
Urticaria	1	0	0
Rash	9 (0.3)	3 (0.1)	6 (0.8)
Swelling face	1	0	0

- Rash – Frequency of rash across studies was lower in the Flublok group compared to Fluzone. None of the rashes in the Flublok group were serious or severe. The majority were assessed as mild and unrelated to Flublok.
- Urticaria occurred in a 52 year old female four days post-vaccination and concurrent with a corneal abrasion and sinus symptoms. They were assessed as mild and possibly related to Flublok.
- The review revealed two events that were either serious or severe and may have represented hypersensitivity or idiosyncratic reactions due to Flublok:
 - PSC04 Subject#05-03221- b(6) - Pleuropericarditis was an SAE that occurred in a 47 year-old male with a history of hypertension within 11 days of vaccination with Flublok. Please see the case summary in Section 8.1.1.2.3, Clinical Studies.
 - Subject 25-19731- b(6)---is a 22 year old white non-Hispanic female who was vaccinated with Flublok on October 12, 2007. Past medical history included seasonal allergic rhinitis in 2003, exercise-induced symptoms (bronchiole constriction, facial edema, edema of extremities, rash, itchiness, and swelling of the tongue) in 2005, and mild asthma and headaches. She reported Grade 2 redness at the injection site on Day 0 and abrupt onset of swollen lips and tongue 10 hours and 20 minutes following vaccination. She self-medicated with Claritin (loratidine) 10mg and Benadryl 25mg, and the symptoms resolved by Study Day 2. The

- Investigator assessed this event as moderate and possibly related to the study vaccine.
- A third subject (Subject 16-12074- b(6)) experienced a hypersensitivity-type event consisting of dizziness, facial swelling, facial pain, nausea, and pruritis occurring 16 days after vaccination with Flublok which resolved spontaneously without sequelae. The events were assessed by the investigator as not related to the study vaccine. This reviewer concurred with this assessment.
- With the exception of the above cases, the database failed to reveal other hypersensitivity signals or important imbalances between Flublok and the control groups.

In addition to the data from studies submitted to the BLA, the Applicant reported no significant safety concerns identified in 10 additional studies of Flublok conducted by PSC and by the NIH. NIH/NIAID studies included 855 subjects, and study PSC02 (not formally submitted to the BLA) included 156 children. SAE narratives from these studies were submitted to the BLA and reviewed, and did not reveal safety signals related to allergic reactions.

A literature search requested by the reviewer revealed numerous reports of insect cell culture systems being studied over the last few decades in preclinical and clinical development programs for human and animal vaccines and gene therapy. Cervarix is one such vaccine manufactured by using a baculovirus vector and a *Trichoplusia ni* insect cell line. Cervarix is licensed for the prevention of human papillomavirus (HPV) infection in Europe and the U.S. No issues have been raised regarding increased potential for hypersensitivity reactions related to the baculovirus expression vector or the insect cell line. The literature search did not reveal reports raising concerns for hypersensitivity reactions related to the use of the *Spodoptera frugiperda* insect cell culture systems.

Reviewer comment: Flublok will be the first influenza vaccine manufactured in a novel insect cell system. Accordingly, despite the apparent absence of safety signals, additional safety data from prospective trials should be collected in all populations for whom an indication is being requested to further assess the potential for hypersensitivity events and unknown unexpected AEs. Additionally, VAERS monitoring for hypersensitivity reactions should be part of the post-licensure pharmacovigilance plan. In the original BLA submission, the Applicant proposed to conduct an open label Phase 4 trial comparing Flublok to TIV in approximately 100,000 individuals 18 years and older with more severe underlying medical conditions than were eligible for studies included in the BLA. In addition, the Applicant planned to conduct a continuation study in subjects from studies PSC04 and PSC06 to evaluate the safety of Flublok when administered in consecutive years. Please see the 2009 OBE/DE review of the Pharmacovigilance Plan by Patricia Rohan, MD and the updated review by Jane Woo, MD.

Other Events of Significance or Potential Significance

The reviewer queried the datasets and examined more closely events with the following SOC and PTs: *Nervous system disorders, dizziness, syncope, facial palsy, Bell's palsy, headache, migraine, hypoaesthesia, paraesthesia, acute disseminated encephalomyelitis, Guillain-Barre Syndrome, myelitis, neuritis, convulsions, seizure, immune system disorders, hypersensitivity, drug hypersensitivity, allergy, anaphylaxis, hives, urticaria, serum sickness, vasculitis, swelling, angioedema, allergic asthma, anemia, lymphadenopathy, thrombocytopenia, immune thrombocytopenia, arthralgia, myalgia, synovitis, rash, rash pruritic, conjunctivitis and red eyes*. Where a relationship to the study vaccine appeared possible, the Applicant was asked to provide case narratives and CRFs.

Reviewer comment: *Overall, evaluation of the datasets for events of particular interest or potential significance revealed three hypersensitivity/urticarial reactions among Flublok recipients as compared to one among controls. No unusual patterns, trends or safety signals were observed, including neurologic adverse reactions. Hypersensitivity reactions will be included in the Adverse Reactions section of the label. Additional safety data will be requested in all populations (See Section 12, Conclusions Overall, and Section 13, Recommendations).*

Solicited Adverse Events (Reactogenicity)

The frequencies of local and systemic reactogenicity events through Day 7 across trials are summarized in Table 62.

Table 62 Solicited Local and Systemic Reactogenicity Adverse Events* Among Adults 18 Years of Age and Older Across Studies PSC 01, PSC 03, PSC 04, and PSC 06:

Diary Card	Flublok N= 3233	Fluzone control N=735	Placebo control N= 2458
Local – Pain	1192 (37%)	265 (36%)	207 (8%)
Local – Redness	167 (5%)	79 (11%)	50 (2%)
Local – Swelling	163 (5%)	88 (12%)	47 (2%)
Local – Bruising	116 (4%)	36 (5%)	65 (3%)
Systemic – Headache	519 (16%)	104 (14%)	417 (17%)
Systemic – Fatigue	445 (14%)	104 (14%)	361 (15%)
Systemic – Tiredness, lack of energy	105 (3%)	65 (9%)	51 (2%)
Systemic - Muscle pain	342 (10%)	79 (11%)	173 (7%)
Systemic - Joint pain	134 (4%)	44 (6%)	91 (4%)
Systemic – Nausea	174 (5%)	30 (4%)	119 (5%)
Systemic - Chills/shivering	102 (3%)	31 (4%)	74 (3%)
Systemic – Fever	23 (1%)	1 (<1%)	14 (1%)

Source: Tables 14.3.6.2 and 14.3.6.5 Module 5, Volume 1, pp256-259 and 282; 14.3.6.1 and 14.3.6.3, Module 5, Volume 10, pp349 and 353-355; 14.3.6.1 and 17.3.6.7, Module 5, Volume 19, pp396-414; and 14.3.6.2 and 14.3.6.5, Module 5, Volume 26, pp204-206 and 213. Reviewer's evaluation of electronic datasets yielded nearly identical results.

* Swelling, hard swelling, and soft swelling reports from studies PSC01 and PSC03 were combined into the category "Swelling". The "Tiredness, lack of energy" category was reported in addition to "Fatigue" in studies PSC01 and PSC03, and are reported separately in the table.

- The most frequent reactogenicity events among Flublok subjects were local pain, headache, fatigue and myalgia. These rates were very similar between Flublok and Fluzone recipients. Flublok and Fluzone recipients experienced significantly more local injection site pain than did placebo recipients (37% versus 8%). In general, the frequencies of systemic reactions in the Flublok group were not very different from the placebo group.
- The 735 Fluzone recipients reported approximately twice as much injection site redness and swelling and tiredness/lack of energy as their Flublok counterparts. Overall, however, the frequency of reactogenicity events experienced by Flublok subjects across studies was similar to those reported for other TIVs.

Unsolicited Adverse Events

- Overall, the frequencies of Unsolicited AEs were similar between Flublok and control groups. Injection site reactions persisting or occurring after the diary card collection, and therefore reported as Unsolicited AEs, were higher in subjects randomized to receive Flublok. In two studies, fever occurred in a higher proportion of subjects randomized to Flublok. For example, pyrexia was reported in 1.3% of Flublok recipients and in no placebo recipients.
- The most frequently reported Unsolicited AEs across all studies were headache and symptoms of respiratory infection (cough, pharyngolaryngeal pain, nasal congestion, URI, nasopharyngitis). These were followed by diarrhea, injection site erythema, and fatigue. Most events were assessed by the investigators as not related to the study vaccines.

Reviewer comment: *Overall, the frequency of AEs was low and similar between treatment groups. No unusual trends or patterns were observed.*

10.3.3 Dropouts

Table 63 presents all discontinuations across studies through Day 180.

Table 63 Discontinuations Across Studies through Day 180 Contact

Study	Flublok n (%)	Control n (%)
PSC04	295 (13.0)	282 (12.0)
PSC06	2 (0.7)	2 (0.7)
PSC03	8 (2.0)	8 (2.0)
PSC01	2 (1.0)	2 (1.0)

Reviewer comment: *The discontinuation rate 180 days post-vaccination for study PSC04 was unusually high and was disproportionate to the other studies. Most of these subjects were lost to follow-up (11% for Flublok and 11% for placebo). Of the 24 study sites in PSC04, 7 had a lost to follow-up rate of >5%. At the VRBPAC meeting on November 19, 2009, the Applicant explained that in an effort to recruit subjects from socioeconomically diverse groups, some sites and subjects were less adherent to the protocol and dropped out after receiving compensation early in the study. Some members of the VRBPAC felt that a lost to follow-up rate of 11%, despite being equal*

between treatment groups, was a potentially important omission or loss of safety data. The balance in persons lost to follow-up between Flublok and control arms, however, mitigates this concern. Additionally, most participants completed follow-up through Day 28, the period when most acute vaccine-related AEs would be expected to occur (see below).

Discontinuations through Day 28 – PSC04:

Discontinuations through Day 28 in PSC04 are presented in Table 64.

Table 64 Discontinuations through Day 28 Contact – PSC04

Disposition	Placebo n (%)	Flublok n (%)
Completed	2211 (96%)	2249 (96%)
Discontinued	93 (4%)	95 (4%)
-Due to AE	0	0
-Lost to follow-up	85 (3.7%)	88 (3.8%)
-Withdrew consent	2 (<1)	7 (<1)
-Other reasons	6 (<1)	0

Reviewer comment: Although 11% of subjects in study PSC04 had been lost to follow-up by the end of the study (Day 180), 96% of subjects in each treatment group completed the first 28 days of the study. Most vaccine-related hypersensitivity-type events would be expected to occur shortly after vaccination and within this time period.

Discontinuations due to AEs across studies through Day 180:

There were no discontinuations due to AEs in studies PSC01 and PSC06. In PSC03 one Fluzone recipient discontinued due to a cerebral hemorrhage. Table 65 presents discontinuations due to AEs in study PSC04:

Table 65 Discontinuations Due to AEs – PSC04*

Treatment	Subject	Reason for discontinuation	Comments
Flublok	04-02568	Pulmonary embolism/death	n/a
Flublok	05-03321	Pleuropericardial effusion	n/a
Flublok	19-14569	Pregnancy	Miscarriage
Flublok	19-14567	Pregnancy	No AE
Flublok	19-14509	Pregnancy	No AE
Flublok	17-10859	Pregnancy	No AE
Placebo	05-03291	Motor vehicle accident/death	n/a
Placebo	11-08096	Multiple fractures	n/a
Placebo	15-11410	Pregnancy	No AE
Placebo	19-14587	Pregnancy	Termination
Placebo	09-05715	Pregnancy	No AE

*PSC01 and PSC06: no discontinuations due to AEs.

PSC03: one Fluzone recipient discontinued due to cerebral hemorrhage.

- Overall, the dropout rate for any reason through Day 180 was $\leq 2\%$ in studies PSC01, PSC03, and PSC06.

Reviewer comment: Although the dropout rate through Day 180 in study PSC04 was 12-13% (and due primarily to loss of follow-up at 7 of 24 sites), the dropout rate was 4% through Day 28 when most vaccine-related hypersensitivity-type events would be expected to have occurred.

10.4.2 Laboratory Findings

There were no routine clinical laboratories performed for the study other than screening urine pregnancy tests.

10.4.3 Vital Signs

There were no unexpected treatment emergent trends or patterns in vital signs identified following Flublok administration across the four studies.

10.4.4 Demographic Interactions including Gender and Race/Ethnicity

Subanalyses

Subjects 18 to 49 Years of Age

Sub-analyses of gender, race and ethnicity were requested on the safety, immunogenicity and vaccine efficacy data from PSC01 and PSC04 in an IR dated September 9, 2012.

PSC provided an integrated summary of these analyses to FDA on September 28, 2012.

- Females reported more solicited local AEs overall as compared to males, 46.2% (95% CI 42.97, 49.72) vs 35.0% (95% CI 31.55, 38.85) and 13.7% (95% CI 11.85, 15.73) vs 9.9% (95% CI 8.12, 12.09) for Flublok and placebo recipients, respectively. Injection site pain accounted for most of the differences, with 43.5% (95% CI 40.38, 46.93) of female and 32.6% (95% CI 29.31, 36.36) of male Flublok recipients and 9.7% (95% CI 8.18, 11.44) of female and 7.2% (95% CI 5.66, 9.04) of male placebo recipients reporting injection site pain within 7 days of vaccination. The differences in injection site pain and in overall solicited local AEs between female versus male Flublok recipients were statistically significant. Females also demonstrated a trend towards reporting more systemic symptoms overall as compared to males, 36.3% (95% CI 33.39, 39.36) vs 27.2% (95% CI 24.17, 30.60) of Flublok recipients, respectively, and 33.4% (95% CI 30.47, 36.52) vs 23.3% (95% CI 20.45, 26.52) of placebo recipients, respectively. This was true primarily for headache and fatigue in both Flublok and placebo recipients. The trends towards increased headache and overall solicited systemic symptoms in female versus male recipients of Flublok were statistically significant.
- Solicited local and systemic AEs overall, and injection site pain in particular, were reported by more white recipients of Flublok (60.8% and 44.6%, respectively) as compared to other races (blacks 40.1% and 22.4%; Asian/Pacific Islander 53.1% and 38.3%; Alaskan/Native American (37.5% and 0%). Only the differences between white and black races were statistically significant with non-overlapping CI's. Non-Hispanics reported local injection site symptoms more frequently overall than Hispanics (56.6% vs 46.2%, respectively). This was true primarily for injection site pain (40.2% vs 30.6%). However, the differences between non-Hispanic and Hispanic recipients of Flublok had overlapping CI's and were not statistically significant. Differences in solicited systemic symptoms

- across races and ethnicities were not notable. Racial and ethnic trends among recipients of placebo were similar to those observed for recipients of Flublok.
- Severe (Grade 3) solicited AEs were <1% across both genders and all races/ethnicities so that significant differences could not be detected.
 - Unsolicited AEs were reported by more female than male recipients of Flublok overall, 21.1% (95% CI 18.93, 23.45) vs 14.7% (95% CI 12.60, 17.25), respectively, but also by more female than male placebo recipients, 18.9% (95% CI 16.80, 21.30) vs 14.6% (95% CI 12.44, 17.15), respectively. Racial and ethnic differences were too small to draw conclusions. Numbers of specific events categorized by SOC were also too small to observe significant gender, racial or ethnic differences. Severe and serious events occurred in < 1% of subjects in all sub-groups. Most events were assessed as mild (Grade 1) across all sub-groups.

Reviewer comment: In general, the observed gender and racial/ethnic differences in the safety analyses represent trends and do not permit firm conclusions. For those categories where significant differences (non-overlapping CI's) were noted among the Flublok sub-groups, e.g., higher frequencies of Solicited local and systemic AEs and Unsolicited AEs overall in females as compared to males, or higher frequencies of solicited AEs overall in whites versus blacks, similar differences were seen between genders and between whites and blacks among the placebo sub-groups. The Applicant also references a literature review that reported a greater incidence of injection site reactions in females than males for a number of vaccines including TIVs.

Subjects 50 Years of Age and Older

Elderly subjects 65 years and older appeared to have less injection site pain, but more swelling and erythema at the injection site than did subjects less than 65 years of age. Subjects aged 50-64 years appeared to have a greater proportion of injection site pain in study PSC06 in comparison to subjects in other age groups in the other studies.

Reviewer comment: Subanalyses were not requested in these age groups because Flublok will not be approved in persons 50 years and older in this review cycle (see Sections 12 and 13).

10.4.5 Potential Product-Product Interactions

There are currently no data that evaluate simultaneous administration of Flublok with other vaccines. In the absence of these data, if Flublok is to be given at the same time as another injectable vaccine(s), the vaccines should be administered at different injection sites. Flublok should not be mixed with any other vaccine in the same syringe or vial.

10.4.6 Pregnancy and Lactation

- The Applicant did not actively recruit pregnant or lactating females in any of the four studies submitted to the BLA. Subjects were expected to use contraception during the study.
- A total of 37 (1%) of the 2740 female subjects in PSC04 became pregnant during the study; 20 had received Flublok and 17 had received Placebo. Complete follow-up was available for 15 (75%) of the Flublok recipients and for 15 (88%) of Placebo

recipients. There were a total of 3 pregnancies in study PSC01, all in the Flublok group. There were no pregnancies in PSC06 or PSC03. The Applicant's case narratives, electronic datasets, and CRFs were reviewed. There were no AEs among the subjects attributed to Flublok and no congenital anomalies reported in the infants who were followed. The pregnancies were reviewed in detail in the Clinical Studies Section 8.

Reviewer comment: A large body of available data in pregnant women indicates that TIV does not cause fetal harm or affect reproductive capacity, and the potential risks for serious complications of influenza justify recommendations for use in this population. Flublok is a novel product and must be considered independently from other traditional egg-grown TIVs. The reproductive/developmental toxicology reviewer recommended a pregnancy category B for Flublok, based on a reproductive safety study in rats. For further discussion, please see Section 4.2 of this review and the Reproductive/Developmental Toxicology Review.

10.4.7 Overdose

Overdose is considered unlikely because Flublok is supplied in single-dose vials.

10.4.8 Postmarketing Data

Not applicable because Flublok is not licensed anywhere in the world.

10.5 Safety Conclusions

- The safety database for Flublok 135µg consisted of 3233 subjects 18 years and older. 23% of subjects were ≥ 50 years of age, and 13% were ≥ 65 years of age. There were slightly more females than males in the overall population. There was a predominance of Caucasians, but race/ethnicity represented the U.S. population fairly closely.
- There were a total of six deaths across the four studies, two occurring in young previously healthy adults and four occurring in subjects > 65 years of age. The deaths were balanced, three in Flublok recipients, three in control groups, and none appeared related to the study vaccines. Discontinuations due to AEs were relatively few, all occurred after Day 28, and none were definitely related to the vaccines.
- Some members of the VRBPAC felt that a loss to follow-up rate of 11% at Day 180 in study PSC04 was an important loss of safety data especially for rare events. However, discontinuations in PSC04 were balanced between treatment groups, and the majority of the discontinuations were from 7 of the 24 study sites, each of which had a lost to follow-up rate of $>5\%$ by the end of the study. Additionally, the discontinuation and loss to follow-up rates for PSC04 through Day 28 were 4%, and for the other clinical trials these rates were $\leq 2\%$. The reviewer believes that most vaccine-related reactions, including hypersensitivity reactions, were they to occur, would have been captured within the 28 days post-vaccination when the lost to follow-up rate was relatively low.
- Ninety SAEs occurred in 70 Flublok recipients and 90 SAEs in 71 controls across all studies. The vast majority of SAEs occurred in subjects over 65 years of age,

and were assessed as unrelated to the study vaccines. Only 2 SAEs, one in each of 2 Flublok recipients, appear to have been related or possibly related to the vaccine: a case of vasovagal syncope (not uncommon with vaccination) and a case of pleuropericarditis, which one cannot exclude as an adverse reaction related to study vaccine although the biologic plausibility of causality is not apparent.

Reviewer comment: If Flublok is approved, the SAE of pleuropericarditis will be described in the product labeling, Adverse Event Section 6.0. We will request that the Applicant conduct post-marketing safety studies and monitor specifically for pleuropericarditis and hypersensitivity reactions.

- Overall, there was no imbalance in hypersensitivity AE's. There were two events in the Flublok groups versus one event in the control groups that appeared to represent true hypersensitivity reactions: one case of swelling of the lips and tongue in a subject with a history of atopy, and one case of mild urticaria occurring four days post-vaccination. Other rashes were generally mild and balanced across studies.
- Evaluation of the datasets for other events of particular interest or potential significance revealed only a single case of possible recurrent Bell's Palsy in a Flublok recipient who had prodromal symptoms prior to vaccination and whose clinical course was not typical for Bell's Palsy. No other unusual patterns, trends, autoimmune events, or safety signals were observed.
- The most frequent reactogenicity events among Flublok subjects were local pain, headache, fatigue and myalgia. Rates were very similar between Flublok and Fluzone recipients. There may have been a slight trend towards more fever in Flublok recipients as compared to Fluzone in study PSC06, but the overall frequency of fever was low across studies. Overall, the frequencies of reactogenicity events experienced by Flublok subjects were similar to those reported for other trivalent influenza vaccines, and the greater antigen content of Flublok, 135µg, relative to TIV, 45µg, did not appear to cause greater reactogenicity.
- The frequencies of Unsolicited AEs were low across studies and similar between treatment groups. Most events were assessed as mild or moderate and not related to the study vaccine. No unusual trends or patterns were observed.
- For a novel vaccine and in comparison with other licensed products, the safety data are limited by the relatively small size of the database, both total (n=3233), particularly in the elderly (n=436), and by the high lost to follow-up rate by the end of the study (11%). However, given these limitations, the data likely were adequate to detect immediate hypersensitivity reactions and common adverse reactions, although causality would be difficult to assess for events with high background rates. Larger post-marketing studies will be necessary to detect uncommon or rare events as for any new vaccines.
- These issues were discussed at the end of the 2009 review cycle and again during the July 17, 2012 CR review cycle. The review team agreed that a requirement for additional pre-licensure safety data beyond what was agreed upon during pre-

BLA discussions with the Applicant and in the absence of a clear safety signal did not appear to be indicated in adults 18 to 49 years of age. The safety database in older adults is smaller. Both PSC03 and PSC06 enrolled fewer subjects than what was recommended by FDA. In the absence of demonstrated efficacy in these age groups, the reviewer will recommend that additional safety studies be required in adults 50 years and older before approval is granted in these older age groups.

11.0 Additional Clinical Issues

11.1 Directions for Use

- Flublok, Influenza Vaccine, Recombinant Hemagglutinin, will be supplied as a sterile, clear, colorless to slightly opalescent liquid in single-dose (0.5mL) vials for IM injection. The formulation contains no added preservatives or adjuvants.
- Each single dose (0.5mL) contains a total of 135µg of recombinant hemagglutinin (HA), with 45µg of HA from each of the three strains of influenza virus contained in the vaccine.
- Dosage in adults is a single 0.5mL dose for IM injection in the deltoid region of the upper arm.
- The vaccine should be stored and transported refrigerated at 2°C to 8°C (36°F to 46°F). It should not be frozen.

11.3 Special Populations

- Demographic data gathered in each of the four studies included age, gender, race/ethnicity, and history of influenza vaccination in the previous influenza season. For details, please refer to the analyses of demographic data presented for each study in Section 8 and to the overview presented Section 10, Overview of Safety. The overall database was comprised primarily of young healthy adults 18 to 49 years of age (77%). Twenty-three percent of subjects were ≥ 50 years of age and 13% were ≥ 65 years of age. Overall, across studies, the demographics were fairly well representative of the U.S. population. Caucasians and females were somewhat overrepresented. Gender, race and ethnicity are not known to influence the humoral immune response to influenza vaccination, while age, immunocompromised states, and previous influenza immunization may affect this response.

Geriatrics

- The BLA provided immunogenicity and safety source data for 436 medically stable subjects ≥ 65 years of age (PSC03) and in 300 healthy adults 50-64 years of age (PSC06). In addition, the Applicant provided a synopsis of study DMID 03-119 (IND 11244) conducted by the DMID/NIAID/NIH. This study provided supportive data for 300 healthy adults ≥ 65 years of age who received Flublok (total of 45, 135, or 405µg) during the 2003-2004 influenza season. The safety data reported in this latter study was similar to results noted for Flublok and TIV in the four studies submitted to the BLA.
- The ability to achieve a post-vaccination HAI titer of ≥ 1:40 was demonstrated in over 80% of subjects in both studies PSC03 and PSC06, including for the B

- strain. SCRs against the B strain, however, missed endpoints, and non-inferiority to TIV could not be demonstrated in adults ≥ 65 years of age (PSC03). The lower immune responses to the B strain, particularly among the elderly, have been observed with other TIVs.
- Clinical endpoint data demonstrated reasonably good point estimates of vaccine efficacy against mismatched type A (predominantly H3N2) and type B influenza in young healthy adults. Data from PSC03 and PSC06 were not sufficient to draw conclusions regarding VE in adults over 50 years of age.

Reviewer comment: The source data in subjects 50 years and older is limited by the small size of the safety database for a novel vaccine, persistent concerns regarding the HAI assay, and insufficient clinical efficacy data in this population. These issues will be discussed further in Sections 12 and 13, Conclusions Overall and Recommendation.

Pediatrics

- The Pediatric Research Equity Act (PREA) of 2003 requires that clinical studies be conducted in children for biological products under development. There must be adequate data to support safety and effectiveness, dosing and administration in this population. Effectiveness may be extrapolated from adequate and well-controlled studies in adults provided that the data is supplemented by safety and surrogate endpoint studies in children. Required pediatric studies in the BLA process may be deferred as long as a postmarketing commitment to conduct Phase IV trials is made. The Applicant submitted a detailed Pediatric Plan on July 17, 2009 (STN 125285/0.18) that included a request to waive studies in children less than 6 months of age and defer studies in children and adolescents 6 months to less than 18 years of age. This plan was presented to the Pediatric Review Committee (PeRC) on December 2, 2009 and was approved. Details of the 2009 plan are not presented because the Applicant submitted an updated Pediatric Plan on August 31, 2012 (STN 125285/0.60) and a revision of the updated plan on September 13, 2012 (STN 125285/0.61) with the July 17, 2012 CR.
- The updated plan contained a new request for a partial waiver in children less than 35 months of age based the very low immunogenicity observed in children 6 months to 35 months of age in study PSC02 following two doses of either the 66.7mcg or 135mcg dose levels of Flublok as compared to Fluzone (data not shown). Immune responses were lowest in the youngest age subset (6-18 months), in children whose baseline HAI titers were $< 1:10$, and against the B strain. There was no clear dose effect. Additionally, the Applicant stated that reactogenicity for the 135mcg dose was significantly greater in Flublok recipients as compared to Fluzone recipients.

Reviewer comment: Given the low immunogenicity observed in children 6-35 months of age, FDA agreed with the request for a waiver in children less than 3 years of age because there is strong evidence that Flublok is not likely to be effective in this age group.

Requests for deferral of studies in children 3 to < 6 years and 6 to < 18 years of age:
The Applicant submitted protocol synopses for 2 proposed pediatric studies summarized in Table 65:

Table 65 Proposed Deferred Pediatric Postmarketing Studies

Parameter	PSC08	PSC14*
Age	6 to <18yrs	3 to <6yrs
Protocol submission	April 30, 2013	June 30, 2015
Completion	November 30, 2014	June 30, 2016
CSR	November 30, 2015	June 30, 2017
Duration	208 days	208 days
Design	Phase 3, MDB, active-controlled, multicenter trial to evaluate the safety, reactogenicity and immunogenicity of Flublok in 720 children 6 years through 17 years of age stratified by age (6-8 years, 9-11 years, and ≥ 12 years), randomized 1:1 to receive Flublok 135mcg or TIV 45mcg.	Phase 3, MDB, active-controlled trial multicenter trial to evaluate the safety, reactogenicity and immunogenicity in 750 healthy children 3 years through 5 years of age randomized 1:1 to receive Flublok 135mcg or TIV 45mcg.
Immunogenicity Endpoints	SCRs and GMTs	SCRs and GMTs
Efficacy Analyses	Non-inferiority of SCR difference and GMT ratios of Flublok to Fluzone	Non-inferiority of SCR difference and GMT ratios of Flublok to Fluzone
Safety endpoints	Solicited , Unsolicited, and Serious AEs	Solicited , Unsolicited, and Serious AEs

*PSC14 was named PSC12 in the Applicant's original pediatric plans but was subsequently renamed.
CSR=complete study report; MDB=modified double-blind; SCRs=seroconversion rates; GMTs=geometric mean ratios.

Reviewer comment: Study PSC14 will be conducted if PSC08 demonstrates sufficient safety and immunogenicity in the older age group. A statistical review will be obtained when the formal protocols and SAPs are submitted.

- Clinical Endpoint Study: In their pediatric plan, the Applicant states that, if PSC08 and PSC14 demonstrate non-inferiority, an efficacy trial may be conducted outside the U.S. as has been requested by the European Medicines Agency (EMA). The Applicant states that, because this is not feasible in the U.S. due to ACIP recommendations for universal vaccination, efficacy in children would be extrapolated by bridging of immunogenicity data to adult data.

Reviewer comment: It would be of interest to review data from a clinical endpoint trial in children. On October 22, 2012, the Office of Pediatric Therapeutics shared with OVRP the EMA plan to conduct two pediatric studies of Flublok in the European Union (EU). The first EU study, also called PSC08, would be similar to the proposed U.S. PSC08, a randomized active-controlled study of 600 children 6 to < 18 years of age to evaluate the safety and immunogenicity of Flublok as compared to a licensed TIV. The second EU study, PSC09, would be a randomized, observer-blind, clinical efficacy trial to evaluate the safety, immunogenicity, and clinical efficacy of Flublok versus a non-influenza vaccine in the prevention of laboratory-confirmed influenza illness in 6,300 children 6 to < 18 years of age. Flublok has not yet been approved in

adults in the EU. FDA contacted PSC on November 29, 2012 to determine whether the Applicant intends to use clinical endpoint data from PSC09 in the U.S. label. PSC indicated that PSC09 would be conducted only if EU PSC08 clearly demonstrated the non-inferiority of Flublok to TIV and that both European studies were intended to support licensure in the U.S. FDA should, therefore, review the study protocol and SAP for PSC09 and eventually review source data if results may be included in the U.S. label. Because the EU PSC08 will compare Flublok to a non-U.S.-licensed TIV, FDA would not include these immunogenicity data in our label. However, FDA would be interested in reviewing summary safety data from the EU PSC08. The Applicant has agreed to provide the results of EU PSC09 if it is conducted and to submit the results of the EU PSC08 IND11951 when available. These EU studies are neither PMCs nor PMRs.

Reviewer comment: The EMA pediatric plan does not change the current plan for non-inferiority studies to support U.S. licensure. These two studies, U.S. PSC08 and PSC14 will be PMRs.

- PeRC meeting for Flublok: PSC's updated pediatric plan was presented to the PeRC on October 24, 2012. The committee agreed with the proposal to waive studies of Flublok in children < 3 years of age on the basis that there is strong evidence to suggest that Flublok would not be effective in this population [Section 505B(a)(4)(B)(ii) of PREA]. The PeRC also agreed with the proposal to defer studies in children 3 to < 18 years of age on the basis that adult studies were complete and Flublok is ready for approval. The committee felt that, if the pediatric studies met their immunogenicity endpoints, the immunogenicity data from these studies in children can be used to bridge to the adult vaccine efficacy data and to extend the age indication for Flublok based on the pediatric non-inferior immunogenicity data. The PeRC was aware that a clinical endpoint trial in children is planned by the EMA. However, the committee did not propose that FDA recommend a pediatric clinical endpoint trial as a PMC for U.S. licensure of Flublok.

Immunocompromised Individuals

- In April 2009, the Applicant submitted a protocol under IND 11244 to conduct a phase 2 study to compare immunogenicity and safety of high dose Flublok (135µg per strain) against TIV in bone marrow transplant recipients. Results are not available. Therefore, at this time no specific recommendations can be made regarding Flublok's use in immunocompromised individuals.

12 Conclusions – Overall

- In healthy adults 18 through 49 years of age, the data submitted to support licensure demonstrated a degree of clinical efficacy against antigenically mismatched strains that, while not meeting the pre-specified criteria for the primary endpoint, appears comparable to data reviewed by FDA for other licensed TIVs and suggests that Flublok would be at least as effective against antigenically matched influenza strains. The total safety database across studies is relatively small for a novel vaccine. However, the safety profile is acceptable and no clear

safety signals have been identified. If approved, Flublok, will be the first U.S. licensed influenza vaccine manufactured completely without the use of eggs, making influenza vaccination available to persons with severe egg allergies. Additionally, because the manufacturing process is not dependent on growing the vaccine-strain viruses in eggs, Flublok may offer another advantage over traditional egg-derived TIVs by the potential for more rapid manufacture and scale up of production in response to unexpected changes in circulating influenza virus strains. Therefore, the reviewer has determined that approval of Flublok should be recommended in persons 18-49 years of age with commitments to collect additional post-licensure safety data.

- In adults 50 years of age and older, Flublok elicited lower immune responses against the B strain that failed to demonstrate non-inferiority to Fluzone in persons 65 years of age and older. Additionally, the data are limited by HAI assay concerns and difficulty in bridging immunogenicity data to vaccine efficacy in younger adults from a trial that failed to meet the pre-specified criteria for the primary clinical endpoint against antigenically matched strains. Based on the data submitted to this BLA, the uncertain effectiveness of Flublok in adults 50 years of age and older and the much smaller safety database in this population are not sufficient to support licensure in this age group at this time. An additional clinical endpoint study will be recommended to support extension of the approved use of Flublok to these older populations (50-64 years and ≥ 65 years of age).

12.1 VRBPAC Recommendations

Contributing to CBER's decision to limit full approval to persons 18-49 years of age is the opinion of the November 19, 2009 VRBPAC (Table 66):

- The Flublok data clearly supported efficacy only in persons 18-49 years of age (9 members agreed, 2 disagreed);
- Division on whether data supported safety in persons 18 years of age and older (5 members agreed, 6 disagreed).

Table 66: 2009 VRBPAC Decision

VRBPAC question	Age group (yrs)	Vote yes	Vote no	Abstain
Does data support efficacy?	18-49	9	2	0
Does data support efficacy?	50-64	5	6	0
Does data support efficacy?	≥ 65	2	9	0
Does data support safety?	≥ 18	5	6	0

- The 6 to 5 votes against effectiveness in persons 50 to 64 years of age, and 9 to 2 against effectiveness in persons 65 years and older stemmed primarily from the low immune responses to the B strain. Flublok's vaccine efficacy against antigenically dissimilar strains in persons 18 to 49 years of age was regarded favorably.
- The committee was divided regarding the safety of Flublok, with 6 to 5 votes against the data being sufficient to support safety:
 - Dr. Thomas Flemming, the statistical expert on the committee, stated that one SAE such as pleuropericarditis, despite uncertainty regarding

attribution, negatively impacted the risk benefit ratio in young healthy adults whose complications from influenza are generally not serious. Dr. Flemming also noted that the discontinuation rate of 11% in PSC04 represented an important omission of data.

- The committee noted that there might be a weak signal for hypersensitivity or immune-mediated events, and that the safety database should be larger for all age groups, particularly in the elderly. More data regarding hypersensitivity with repeat vaccination was recommended.
- Because licensed alternative TIVs are available, and because Flublok's vaccine efficacy was not felt to be well-established, the committee was divided on whether Flublok's risk benefit ratio was favorable. Some members recommended that a higher bar for safety should be set because Flublok is a novel vaccine, and one member cautioned against mass vaccinations without more pre-licensure safety data.

Reviewer comment: The rates of hypersensitivity type events across studies did not reveal an imbalance between Flublok and controls. A larger safety database may be needed to detect this theoretical risk.

13.0 Recommendations:

13.1 Approval with Postmarketing Requirements and Commitments

- Full ("traditional") approval is recommended for Flublok in persons 18 to 49 years of age. Approval should be contingent upon the Applicant's agreement to conduct: 1) a large Phase 4 observational postmarketing safety study in persons 18 to 49 years of age aimed at evaluating the potential for Flublok to cause less common adverse events (a PMC); and 2) pediatric studies as required by PREA, outlined in Sections 11.3 and 13.2 (PMRs).
- Full ("traditional") approval in adults 50 to 64 of age and 65 years and older is not recommended because of insufficient safety, immunogenicity, and clinical efficacy data. Approval in these age groups will require additional post-licensure safety and effectiveness data.

13.2 Recommendations on Post-Marketing Actions

The Applicant has agreed to the following post-marketing requirements:

- Deferred pediatric study under PREA (PSC08) to evaluate the safety, reactogenicity, and immunogenicity of Flublok in healthy children 6 to 17 years of age (final protocol to be submitted April 30, 2013, study completed by November 30, 2014, CSR submitted by November 30, 2015).
- Deferred pediatric study under PREA (PSC14) to evaluate the safety, reactogenicity, and immunogenicity of Flublok in healthy children 3 to 5 years of age (final protocol submitted by June 30, 2015, study completed by June 30, 2016, CSR submitted by June 30, 2017).

The Applicant has agreed to the following post-marketing commitments:

- A Phase 4 post-marketing safety study in adults 18-49 years of age under a protocol with pre-specified statistical analyses (final protocol submitted by March 31, 2013, study completed by May 31, 2014, and CSR submitted by May 31, 2015).
- A prospective and comprehensive pregnancy registry (final protocol submitted by June 30, 2013, study completed by December 31, 2019, CSR submitted by December 31, 2020).

The Applicant has agreed to the following non-PMR/PMC requests:

- To provide the CSR for the EMA pediatric safety and immunogenicity study (also named PSC08) to IND 11951 when available. To be initiated 3Q2013, completed 3Q2014, CSR submitted by 4Q2015.
- To provide the results of the pediatric clinical efficacy study, PSC09, described in the EMA Pediatric Plan, if conducted. Final protocol to be submitted by June 30, 2016, study completed by June 30, 2018, CSR submitted by June 30, 2019.
- To support licensure in persons 50 years of age and older, PSC has agreed to conduct in this age group 1) a safety study to begin in January or February 2013, and 2) a clinical endpoint study to be initiated in the fall of 2013. A protocol and protocol synopsis for the respective studies have been submitted to IND 11951 Amendment 65 and are under review.

13.3 Labeling

- FDA sent proposed revisions to PSC's first draft Package Insert (PI) to the Applicant on November 9, 2012. FDA's major revisions to the Applicant's draft were to remove all clinical data from PSC03 and PSC06 and to remove immunogenicity data in adults 18-49 because of concerns over the HAI assay and interpretation of HAI titers using BEVS-derived antigens (see Section 4.4). Negotiations concluded on December 21, 2012 when the Applicant submitted final versions of the labeling that were acceptable to FDA.
- Please see the Advertising and Promotional Labeling Branch (APLB) review of the approved proprietary name which will be Flublok (tallman B eliminated).