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BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125285.194
CBER Received Date	December 4, 2015
PDUFA Goal Date	October 7, 2016
Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name	Cynthia Nolletti
Review Completion Date / Stamped Date	July 11, 2016 October 3, 2016
Supervisory Concurrence	Meghan Ferris, MD, MPH Team Leader, CRB2
	Andrea Hulse, MD Chief, CRB2
Applicant	Protein Sciences Corporation
Established Name	Quadrivalent Influenza Vaccine
Trade Name	Flublok Quadrivalent
Pharmacologic Class	Vaccine
Formulation	Each 0.5mL dose contains 45µg recombinant hemagglutinin (rHA), total 180µg, from each of the recommended influenza types and subtypes: • A/H1N1 • A/H3N2 • B/Yamagata • B/Victoria
Dosage Form and Route of Administration	Sterile solution for intramuscular (IM) injection supplied in single dose 0.5mL pre-filled syringes.
Dosing Regimen	A single 180mcg/0.5 mL dose IM
Indication and Intended Population	Active immunization against disease caused by the influenza virus subtypes A and types B contained in the vaccine. For use in persons ≥18 years of age.
Orphan Designated	No

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GLOSSARY

ACIP	Advisory Committee for Immunization Practices
AE	adverse event
AESI	adverse event of special interest
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	complete study report
DSMB	data safety monitoring board
EP	Evaluable Population
ES	Executive Summary
FAS	full analysis set
FDAAA	Food and Drug Administration Amendments Act of 2007
GMT	geometric mean titer
HA	hemagglutinin
HI	hemagglutination inhibition
IIV	inactivated influenza vaccine
IIV3	trivalent inactivated influenza vaccine
IIV4	quadrivalent inactivated influenza vaccine
IM	intramuscular
ISE	integrated summary of efficacy
ITT	intent-to-treat
LAIV	live attenuated influenza vaccine
LB	lower bound
MAE	medically attended event
mcg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NA	neuraminidase
NH	Northern Hemisphere
NI	non-inferiority
OBE	Office of Biostatistics and Epidemiology
OBE/DE	Office of Biostatistics and Epidemiology/Division of Epidemiology
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PMC	postmarketing commitment
PMR	postmarketing requirement
PPP	Per Protocol Population
PREA	Pediatric Research Equity Act
PSC	Protein Sciences Corporation
PSP	Pediatric Study Plan
PVP	Pharmacovigilence Plan
PT	Preferred Term
QIV	quadrivalent influenza vaccine
REMS	risk evaluation and mitigation strategy

RIV	recombinant influenza vaccine
RIV4	quadrivalent recombinant influenza vaccine
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SCR	seroconversion rate
SOC	system organ class
SP	Safety Population
TEAE	treatment emergent adverse event
TIV	trivalent influenza vaccine
VAERS	Vaccine Adverse Event Reporting System
VRBPAC	Vaccine and Related Biologics Products Advisory Committee
UB	upper bound

1. Executive Summary

Flublok Quadrivalent (also referred to as Flublok RIV4 in this review) is a recombinant influenza vaccine, manufactured in a baculovirus expression vector and insect cell culture system, consisting of four recombinant influenza hemagglutinin (HA) antigens derived from influenza virus type A, subtypes H1 and H3, and two type B virus strains. Hemagglutinin genes from each of the four influenza viruses are inserted into a plasmid baculovirus expression vector system (BEVS) and expressed in *Spodoptera frugiperda* insect cells. Flublok Quadrivalent is indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine, for use in adults 18 years and older, and is manufactured by the same process as Flublok trivalent influenza vaccine (TIV), originally approved on January 16, 2013 in adults 18 through 49 years. Unlike the trivalent formulation, Flublok Quadrivalent contains two B virus strains, one from each of two phylogenetic lineages. Quadrivalent influenza vaccines mitigate against the potential for antigenic mismatch and poor efficacy associated with an incorrect prediction of which B lineage virus will predominate in a given influenza season. The dosing regimen of Flublok Quadrivalent in adults is one dose of 180µg [45µg per recombinant hemagglutinin (rHA) antigen] administered intramuscularly (IM). In an early phase dose-finding study PSC determined that 45 µg per rHA was required for an optimal immune response when compared to 15 µg rHA.

Protein Sciences Corporation (referred to as PSC or "the Applicant" in this review) submitted the efficacy supplement, STN 125285/194, to support an indication for Flublok Quadrivalent in adults 18 years and older and to fulfill a postmarketing requirement (PMR) to conduct a clinical endpoint study of Flublok (trivalent) in adults 50 years and older. Following its original approval in January 2013 for adults 18 through 49 years, Flublok TIV was granted accelerated approval (21 CFR 601, Subpart E) in adults ≥50 years based on immunogenicity data with a PMR to conduct a clinical endpoint study to confirm benefit in this population. Subsequent to approval in older adults, PSC began clinical development of Flublok Quadrivalent, and CBER agreed that the PMR study in older adults to verify clinical benefit could be conducted with the quadrivalent formulation.

PSC submitted two studies to STN 125285/194 to support the safety and effectiveness of Flublok Quadrivalent in adults ≥18 years: PSC16 (adults 18 through 49 years) and PSC12 (adults ≥50 years).

PSC16 was a Phase 3, observer-blind, randomized, comparator-controlled, multicenter trial, conducted in the Northern Hemisphere (NH) 2014-2015 influenza season, to evaluate the safety, reactogenicity, and immunogenicity of Flublok Quadrivalent as compared to a U.S.-licensed quadrivalent inactivated influenza vaccine (IIV4) in ambulatory, medically stable adults 18-49 years of age. The U.S.-licensed comparator used in this study was Fluarix Quadrivalent (also referred to as IIV4 in this review), manufactured by GlaxoSmithKline. A total of 1350 subjects were enrolled and randomized 3:1 to receive a single dose of Flublok Quadrivalent (180 mcg) or IIV4 (60 mcg) IM. Immune responses were assessed by measuring hemagglutination inhibition (HI) antibody titers to each of the four influenza virus antigens contained in the vaccines, collected prior to vaccination on Day 0 and at 28 days post-vaccination. HI titers are currently the best available surrogate marker of activity reasonably likely to predict the clinical benefit of influenza vaccines. Antigens used in the HI assay in both PSC16 and PSC12 were derived from viruses grown in eggs.

PSC16 pre-specified eight co-primary immunogenicity endpoints: HI geometric mean titers (GMT) and seroconversion rates (SCR) at post-vaccination Day 28 for each of the four vaccine antigens in each treatment group. Seroconversion was defined as either a pre-vaccination HI titer of < 1:10 and a post-vaccination HI titer of ≥ 1:40, or a pre-vaccination HI titer of ≥ 1:10 and a minimum 4-fold rise in post-vaccination HI titer at Day 28. The pre-specified success criteria for establishing non-inferior immunogenicity of Flublok Quadrivalent as compared to IIV4 were, for all four vaccine antigens:

- Upper bound (UB) of the 2-sided 95% confidence interval (CI) for GMT_{IIV4} / $GMT_{Flublok} \leq 1.5$, *AND*
- UB of the 2-sided 95% CI for $SCR_{IIV4} - SCR_{Flublok} \leq 10\%$.

Secondary endpoints included SCRs and the proportion of subjects with HI titers ≥ 1:40 (% ≥ 1:40) at post-vaccination Day 28 for all four antigens in each treatment group. For each study vaccine, secondary immune response endpoints were met if, for all four antigens, the lower bound (LB) of the 2-sided 95% confidence interval (CI) for the SCR was ≥ 40% and the LB of the 2-sided 95% CI for the % ≥ 1:40 was ≥ 70%. Exploratory analyses of immunogenicity and safety included subpopulation analyses according to sex, race, and ethnicity.

PSC12 was a Phase 3, randomized, observer-blind, comparator-controlled, multicenter clinical trial conducted in the NH 2014-2015 influenza season to evaluate the vaccine efficacy (VE), immunogenicity, safety, and reactogenicity of Flublok Quadrivalent as compared to IIV4 in ~9000 ambulatory, medically stable adults ≥50 years of age. To ensure balanced enrollment across age and treatment groups, the sponsor used a software program to cap enrollment for the entire study, each site, and for each of three age subgroups: 50-64, 65-74, and ≥75 years of age. Subjects were randomized 1:1 to receive a single dose of Flublok Quadrivalent 180mcg or U.S.-licensed Fluarix Quadrivalent (IIV4) 60mcg. For the primary analysis, relative vaccine efficacy (rVE), calculated as [1 – (Flublok RIV4 attack rate / IIV4 attack rate) x 100], was based on reverse transcriptase polymerase chain reaction (rt-PCR)-confirmed influenza (all strains regardless of antigenic similarity to vaccine antigens) associated with protocol-defined influenza-like illness (ILI). Cases of ILI were collected actively and passively from 14 days post-vaccination through the end of the influenza season. Non-inferior VE was pre-specified as a LB of the 2-sided 95% CI for the rVE of Flublok Quadrivalent vs IIV4 of greater than -20% [non-inferiority (NI) margin of -0.20]. If NI criteria were met, the protocol (but not the statistical analysis plan) pre-specified an exploratory criterion for

superiority of a LB of the 2-sided 95% CI for rVE of > +9%. Secondary efficacy endpoints included analyses of rVE against antigenically similar influenza strains using culture-confirmed ILI and CDC-defined ILI. The non-inferior immunogenicity of Flublok Quadrivalent as compared to IIV4 was also assessed in a subset of subjects by evaluating HI titers on Days 0 and 28 collected from subjects (n=614) enrolled at five pre-specified study sites. The secondary immunogenicity analyses of GMT ratios and SCR differences were evaluated using the same success criteria as were used in PSC16. Exploratory endpoints included subpopulation analyses of rVE and immunogenicity according to age groups, sex, race and ethnicity.

The safety database submitted to support licensure of Flublok Quadrivalent in adults 18 years and older was derived from two studies, PSC16 and PSC12, which provided safety data for a total of 10,002 subjects: 1330 subjects 18-49 years (PSC16) (Flublok RIV4 n=998) and 8672 subjects ≥50 years (PSC12) (Flublok RIV4 n=4328), for a total of 5326 subjects who received a single 180mcg dose of Flublok Quadrivalent and 4676 subjects who received a single 60mcg dose of IIV4. To evaluate safety, both studies actively solicited local and systemic reactogenicity events for 7 days, collected unsolicited adverse events (AEs) for 28 days, and collected both serious adverse events (SAEs) and medically-attended events (MAEs) for 6 months post-vaccination. Safety was summarized using descriptive statistics.

Summary of Immunogenicity and Efficacy

The Immunogenicity Population for PSC16 included a total of 1292 subjects, of whom 969 received Flublok Quadrivalent and 323 IIV4. Tables 1 and 2 present results of co-primary endpoints and non-inferiority analyses for HI GMTs, GMT ratios, SCRs and SCR differences for each antigen contained in the study vaccines. Flublok Quadrivalent met pre-specified success criteria for non-inferior post-vaccination GMTs and SCRs relative to IIV4 for both influenza A strains and for B/Yamagata but not for the B/Victoria lineage strain (UB of the 95% CI for the GMT ratio of 1.71; UB of the 95% CI for the SCR difference of 23.9%).

Table 1: Day 28 Post-vaccination HI GMTs and GMT ratios for Flublok Quadrivalent Relative to IIV4 in Adults 18 through 49 Years of Age – PSC16 (Immunogenicity Population)

Strain	**RIV4 GMT (95% CI) N=969**	**IIV4 GMT (95% CI) N=323**	**GMT Ratio (95% CI)**	**Met GMT NI Criteria?***
A/H1N1	493 (460,537)	397 (358,441)	0.81 (0.71,0.92)	Yes
A/H3N2	748 (700,800)	377 (341,417)	0.50 (0.44,0.57)	Yes
B /Yamagata	156 (145,168)	134 (119,151)	0.86 (0.74,0.99)	Yes
B/Victoria	43 (40,46)	64 (57,71)	1.49 (1.29,1.71)	No

Source: STN 125285/194.9, Module 5, PSC16 CSR, Table 14.2.1.1.1 (07Mar2016).
Abbreviations: HI=hemagglutinin inhibition; RIV4=Flublok Quadrivalent; IIV4=Fluarix Quadrivalent; GMT=geometric mean titer.
*Success criteria for the GMT ratio (GMT_{IIV4} / GMT_{RIV4}): UB of the 95% CI must be ≤ 1.5.

Table 2: Day 28 Post-vaccination HI SCRs and SCR differences between Flublok Quadrivalent and IIV4 in Adults 18 through 49 Years of Age – PSC16 (Immunogenicity Population)

Strain	RIV4 SCR N=969 % (95% CI)	IIV4 SCR N=323 % (95% CI)	SCR Difference % (95% CI)	Met SCR NI Criteria?*
A/H1N1	66.7 (63.6,69.6)	63.5 (58.0,68.7)	-3.2 (-9.2,2.8)	Yes
A/H3N2	72.1 (69.2,74.9)	57.0 (51.4,62.4)	-15.2 (-21.3,-9.1)	Yes
B /Yamagata	59.6 (56.5,62.8)	60.4 (54.8,65.7)	0.7 (-5.4,6.9)	Yes
B/Victoria	40.6 (37.4,43.7)	58.2 (52.6,63.6)	17.6 (11.4,23.9)	No

Source: STN 125285/194.9, Module 5, PSC16 CSR, Tables 14.2.1.2 (07Mar2016).
Abbreviations: HI=hemagglutinin inhibition; RIV4=Flublok Quadrivalent; IIV4=Fluarix Quadrivalent; SCR=seroconversion rate.
*Success criteria for the SCR difference (SCR_{IIV4} - SCR_{RIV4}): UB of the 95% CI must be ≤ 10%.

The Efficacy Population for PSC12 included a total of 8605 subjects of whom 4303 received Flublok Quadrivalent and 4301 IIV4. Table 3 presents results of the primary endpoint analysis, the rVE of Flublok Quadrivalent against rt-PCR-confirmed, protocol-defined ILI due to all virus strains (regardless of antigenic similarity between vaccine and isolate) as compared to IIV4.

Table 3: Relative Vaccine Efficacy of rt-PCR-Confirmed ILI Due to All Influenza Virus Strains – PSC12 (Efficacy Population)

Flublok RIV4 N=4303	Flublok RIV4 N=4303	IIV4 N=4301	IIV4 N=4301	RR	rVE (95% CI)
n (#of cases)	Attack Rate	n (# of cases)	Attack Rate	$AR_{Flublok}/AR_{IIV4}$	(1 - RR) x 100
96	2.2	138	3.2	0.70	30% (10%, 47%)

Source: STN 125285/194.9, Module 5, PSC12 CSR, Table 14.2.1.1 (03Mar2016)
Attack Rate (AR) = # of cases of ILI / # subjects in the treatment group
Relative Risk (RR) = AR Flublok RIV4 / AR IIV4
Relative Vaccine Efficacy (rVE) of Flublok RIV4 versus IIV4 = (1 – RR) x 100

Flublok Quadrivalent met the pre-specified success criteria for non-inferior vaccine efficacy relative to IIV4, i.e., the LB of the 95% CI of rVE must be greater than –20%.

Secondary rVE analyses based on rt-PCR-confirmed and culture-confirmed CDC-defined ILI also met NI criteria. These analyses were based on fewer confirmed cases of ILI, probably due to the lower sensitivity of culture-confirmation and a more stringent CDC definition of ILI in identifying influenza.

The Applicant was unable to provide pre-specified secondary analyses according to antigenic or phylogenetic similarity of vaccine antigen to clinical isolates. However, CDC surveillance from November 2014 through April 2015 indicated that ~83% of wild type influenza isolates from medically-attended outpatient cases of ILI were identified as influenza A/H3N2, which predominated until the end of February 2015, and most of these isolates were antigenically distinct ("mismatched") from recommended vaccine strains, resulting in an unusually low estimate of vaccine effectiveness for A/H3N2 [13% (95% CI: 2%, 23%) for all age groups]. In contrast, wild type influenza A/H1N1, B/Yamagata, and B/Victoria were antigenically similar or well-matched to recommended vaccine strains. Influenza B comprised ~17% of all isolates for the season (85% B/Yamagata and 15% B/Victoria), and B/Yamagata predominated from the end of February through May 2015. [15,16] The Applicant conducted post hoc exploratory

analyses of rVE according to influenza type A or B. Although these analyses were not powered for statistical significance, they show a trend towards non-inferior rVE for Flublok Quadrivalent against influenza A but not for influenza B where the number of cases were fewer and 95% CIs wider: the rVE for influenza A (all A/H3N2) was 36% (95% CI: 14, 53) and for influenza B 4% (95% CI: -72, 46).

The Immunogenicity Population in PSC12 included a total of 614 subjects, of whom 314 received Flublok Quadrivalent and 300 IIV4. Flublok Quadrivalent met success criteria for both non-inferior SCR differences and GMT ratios for the influenza A/H3N2 and B/Yamagata vaccine antigens but failed to meet criteria for the SCR difference for A/H1N1 and for both the SCR difference and GMT ratio for B/Victoria.

Summary of Safety

In the two studies (PSC16 and PSC12) submitted to support licensure, a total of10,002 subjects provided safety data, Flublok Quadrivalent n=5326 and IIV4 n=4676. Among all subjects, 13.3% were 18-49 years, 51.8% 50-64 years, and 34.8% ≥65 years. Demographic characteristics were balanced between treatment groups in both studies. Among all subjects, 59.3% were female, 77.5% white/Caucasian, 20.2% black/African American, 93.5% non-Hispanic/Latino ethnicity, and 6.4% Hispanic/Latino ethnicity. Other racial groups each comprised <1% of the total safety database.

No deaths or discontinuations due to AEs occurred in PSC16 (adults 18-49 years). Twenty subjects died in PSC12 (adults ≥50 years) during the six month post-vaccination study period, Flublok Quadrivalent n=8, IIV4 n=12. The clinical reviewer agreed with the investigator and Applicant's assessments that all deaths were unrelated to study vaccine.

In adults 18-49 years (PSC16), SAEs occurred in ten (1.0%) Flublok Quadrivalent and two (0.6%) IIV4 recipients during the six months post-vaccination and, of these, three (0.6%) Flublok Quadrivalent recipients had three SAEs while no IIV4 recipients had SAEs during the 28 days post-vaccination. The clinical reviewer agreed with the investigators and Applicant's assessments that none of the SAEs appeared related to study vaccines.

In subjects ≥50 years (PSC12), a total of 145 (3.4%) and 132 (3.0%) subjects in the Flublok Quadrivalent and IIV4 treatment groups, respectively, experienced SAEs over the six month safety follow-up period. Of these subjects, 25 (0.6%) and 22 (0.5%) Flublok Quadrivalent and IIV4 recipients, respectively, reported SAEs in the 28 days post-vaccination. The types and frequencies of SAEs were balanced between treatment groups. Most SAEs were events that occur commonly in an older adult and elderly population, and, in the opinion of the reviewer, none appeared clearly related to study vaccines. Other than an imbalance of ILIs (more in IIV4 recipients), medically-attended events (MAEs) were balanced between treatment groups.

During the six months post-vaccination, no subjects 18-49 years (PSC16) or ≥50 years (PSC12) experienced adverse events of special interest (AESIs), potential risks associated with influenza vaccines and defined in the sponsors pharmacovigilance plan (PVP), other than possible hypersensitivity events. Collection of potential hypersensitivity events were not pre-specified but were evaluated post hoc in both studies. Events were mostly mild in severity and non-serious, and, for many, causality uncertain. Rates were low and very small imbalances may have been due to chance

alone. No severe or serious allergic reactions, including anaphylaxis, were reported following administration of Flublok Quadrivalent or IIV4 in either study although, in the reviewer's opinion, one non-serious case of bronchospasm three days following Flublok Quadrivalent in PSC16 might have more appropriately been categorized as severe rather than moderate in intensity. Overall, Flublok Quadrivalent was not associated with a greater risk of clinically significant acute hypersensitivity in the safety database of 5326 adults ≥18 years participating in these two studies.

In both PSC16 and PSC12, the incidence and severity grades of solicited local and systemic reactogenicity events were generally similar between treatment groups and were consistent with what is described in the current Package Inserts. Among adults 18-49 years (PSC16), the most common local reactogenicity events were injection site tenderness (Flublok 47.9%, IIV4 46.7%) and pain (Flublok 36.8%, IIV4 36.4%). The rates of injection site redness were low but occurred more frequently among Flublok recipients as compared to IIV4 (4.2% versus 0.9%). The most common systemic symptoms were headache (Flublok 20.3%, IIV4 21.1%), fatigue (Flublok 16.5%, IIV4 16.6%), muscle pain (Flublok 12.8, IIV4 11.7%), and joint pain (Flublok 9.5%, IIV4 10.2%). Among adults ≥50 years, the most common local reactogenicity events were injection site tenderness (Flublok 34.3%, IIV4 37.1%) and pain (Flublok 18.9%, IIV4 22.0%). The most common solicited systemic symptoms were headache (Flublok12.7%, IIV4 13.5%), fatigue (Flublok 12.2%, IIV4 12.2%), muscle pain (Flublok 8.5%, IIV4 8.8%), and joint pain (Flublok 7.5%, IIV4 8.0%). In both studies most events were mild to moderate (Grade 1 to Grade 2) in severity and short in duration. Severe (Grade 3) reactions were uncommon.

Overall, the safety of Flublok Quadrivalent was acceptable and comparable to IIV4 in adults ≥18 years of age.

Pediatric Research Equity Act (PREA) Considerations

In accordance with PREA regulations, the original approval of Flublok was associated with two deferred postmarketing requirements (PMRs) to conduct studies to evaluate the safety and immunogenicity of Flublok in children and adolescents 6 through 17 years of age (PSC08) and in children 3 through 5 years of age (PSC14). In October 2014, PSC initiated clinical development of a quadrivalent formulation under IND 15784, which triggered PREA due to the new active ingredient (a second influenza type B antigen), and submitted an initial Pediatric Study Plan (iPSP) for Flublok Quadrivalent. Subsequent negotiations with the Applicant resulted in revisions to the PSP that required releasing PSC from the original PSC08 PMR and replacing it with two new PMRs, PSC08 and PSC17 (letter sent to the Applicant on February 2, 2016). STN 125285/194 included a final PSP with requests to defer three studies: PSC08 (Phase 2, 6 through 17 years), PSC17 (Phase 3, 6 through 17 years), and PSC14 (Phase 3, 3 through 5 years). In the revised PSP, the Applicant requested a waiver for studies in children <3 years because previous data demonstrated markedly diminished immunogenicity in this population, suggesting that Flublok would be ineffective in this age group. The Pediatric Review Committee (PeRC) approved the final PSP on March 9, 2016. However, on March 22, 2016, PSC submitted a meeting request to discuss a revised pediatric plan which proposed conducting a single clinical endpoint study of relative VE in children 3 through 17 years in Mexico. This plan was acceptable to the review team, and the Approval Letter for Flublok Quadrivalent will release PSC from the current PSC17 and PSC14 PMRs and re-issue PSC17 as a new phase 3 PMR to evaluate the safety,

immunogenicity and efficacy of Flublok Quadrivalent in children 3 through 17 years. The deferred pediatric PMR, PSC17, will have the following associated timelines:

Final Protocol Submission: January 31, 2018
Study Completion Date: June 30, 2019
Final Report Submission: June 30, 2020

PSC17 will fulfill both the Flublok trivalent and Flublok Quadrivalent PMRs.

Pharmacovigilence Plan – PMCs and PMRs

The original approval of Flublok was associated with a PMC to conduct a large safety study in adults ≥18 (PSC13) and a PMC to initiate a pregnancy registry (PSC15). PSC13 is ongoing and, because the Applicant has indicated that PSC13 has nearly reached its planned enrollment, OBE/DE expects the study to include only recipients of the trivalent formulation. OBE/DE did not identify any safety issues that would warrant a safety-related PMR or Risk Evaluation and Mitigation Strategy (REMS) for Flublok Quadrivalent, and agreed with the Applicant's plan to conduct routine surveillance for the quadrivalent formulation. However, if PSC13, postmarketing safety surveillance, or other sources of data suggest a signal of serious risk or potential for serious risk, then OBE/DE may recommend a phase 4 study to evaluate the safety of Flublok Quadrivalent. Please see the OBE/DE review for further discussion.

The Applicant will initiate a pregnancy registry (PSC15) that will include both recipients of Flublok and Flublok Quadrivalent. However, this PMC will remain associated with the original approval of Flublok. Please see the OBE/DE review for details.

Final Recommendation

Flublok Quadrivalent should be approved in adults 18 years and older with the caveat that the data supporting efficacy and effectiveness in adults ≥65 years are not as robust as compared to younger adults, and efficacy and immunogenicity against influenza B in all age groups was lower as compared to influenza A. However, lower effectiveness in the elderly and against influenza B have also been observed in studies of other influenza vaccines. We also note that influenza vaccine effectiveness depends on multiple variables that change from one season to the next, that no single season provides conclusive data, and that some degree of uncertainty is unavoidable. Given these considerations and provided that CMC issues surrounding potency and stability have been resolved, the reviewer is reasonably satisfied that the data support non-inferior efficacy and immunogenicity for Flublok Quadrivalent relative to IIVs and a favorable risk benefit assessment.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Adults 18-49 Years (PSC16)

Subanalyses of immunogenicity according to sex, black and white race, and Hispanic/Latino ethnicity, in adults 18-49 years, showed results similar to the overall study population. The numbers of subjects representing racial groups other than blacks or whites were too small to draw meaningful conclusions from immunogenicity subanalyses.

Among adults 18-49 years (PSC16), local injection site reactions were reported more frequently among females and whites as compared to males and non-whites [rates of

any solicited local reaction 56.7% and 59.7% versus 41.2% and 40.1%, respectively]. Females reported slightly more systemic symptoms overall as compared to males (38.2% versus 26.8%), the largest difference being in the frequency of headache (23.0% vs 15.6%). There were only small differences in the rates of solicited systemic symptoms between whites and non-whites (rates of any systemic symptom 36.3% vs 30.9%, respectively). Overall, non-Hispanics/Latinos had higher rates of any solicited AE than Hispanics/Latinos (62.8% vs 53.4%, respectively), with local tenderness accounting for much of the difference (49.3% vs 38.8%). The numbers of subjects belonging to racial groups other than whites or blacks or of Hispanic ethnicity were too small for meaningful comparisons of the rates of solicited adverse events in these subpopulations.

Overall, more females than males reported unsolicited AEs (Flublok RIV4 female vs male recipients 11.0% vs 9.2%; IIV4 female vs male recipients 12.2% vs 7.3%). The largest disparity was observed in the category of Infections and Infestations (Flublok RIV4 female vs male recipients 3.3% vs 2.5%; IIV4 female vs male recipients 4.5% vs 0.9%). Rates and severity grades were similar between treatment groups. overall and by body system category. More whites than non-whites reported unsolicited AEs for most body system categories (overall, Flublok RIV4 white vs non-white recipients 13.1% vs 6.4%; IIV4 white vs non-white recipients 13.4% vs 6.2%). The largest disparity was observed in the category of Infections and Infestations (Flublok RIV4 white vs non-white recipients 4.4% vs 1.0%; IIV4 white vs non-white recipients 5.0% vs 0.8%). Rates and severity grades were similar between treatment groups. Blacks/African Americans comprised the majority of non-white racial groups. The incidence and severity of unsolicited AEs in Hispanic/Latinos were similar to non-Hispanic/Latinos.

Subanalyses of deaths and SAEs (PSC16) by sex, race, and ethnicity were limited by the very low numbers of subjects who experienced these events (no deaths and twelve SAEs in the overall safety population), but no trends or large imbalances were observed. Rates of MAEs were higher in females, whites, and non-Hispanic/Latinos as compared to males, non-whites, and Hispanic/Latinos. However, rates were very low and the study was not sufficiently powered to draw definitive conclusions from the trends.

Adults ≥50 Years (PSC12)

Among adults ≥50 years, subanalyses of RE for rt-PCR confirmed protocol-defined ILI according to four different age groups 50-64, ≥65, 65-74, and ≥75 years yielded point estimates of RE of 41%, 17%, 9%, and 37%, respectively, with LBs of the 95% CIs of 15%, -20%, -45%, and -25%, respectively (Table 4).

Table 4: Relative Vaccine Efficacy of rt-PCR- Confirmed ILI Due to Any Influenza Virus Strain according to Age Sub-Group– PSC12 (Efficacy Population)

Age group	RIV4 N=4303*	RIV4 N=4303*	IIV4 N=4301*	IIV4 N=4301*	RR	RE (95% CI)
--	n (#of cases)	Attack Rate	n (# of cases)	Attack Rate	$AR_{Flublok}/AR_{IIV4}$	(1 - RR) x 100
50-64 yrs	44	0.017	76	0.029	0.59	0.41 (0.15, 0.61)
≥65 yrs	52	0.030	62	0.036	0.83	0.17 (-0.20, 0.43)
65-74 yrs	39	0.032	43	0.035	0.91	0.09 (0.-45, 0.40)
≥75 yrs	13	0.025	19	0.040	0.63	0.37 (-0.25, 0.72)

Source: STN 125285/194, Module 5, PSC12 CSR, Tables 14.2.1.1

*Number of subjects in RIV4 and IIV4 age sub-groups, respectively: 50-64 yr (2571, 2591); ≥65 yrs (1732, 1710); 65-74 yrs (1210, 1239); ≥75 yrs (522, 471).
Attack Rate (AR) = # of cases of ILI / # subjects in the treatment group
Relative Risk (RR) = AR Flublok RIV4 / AR IIV4
Relative Efficacy (RE) of Flublok RIV4 versus IIV4 = (1 – RR) x 100

Analyses according to age subgroups showed a trend towards lower rVE for Flublok RIV4 in adults ≥65 years as compared to adults 50-64 years, and, although subgroup analyses lacked statistical power, Flublok in these older age groups did not meet criteria for NI rVE.

In the immunogenicity subset of adults ≥65 years, as compared to adults 50-64 years, a trend towards lower GMTs and SCRs, and higher SCR differences and GMT ratios (i.e., not non-inferior to IIV4) was observed in adults ≥65 years for A/H1N1 and in adults ≥75 years for A/H1N1, A/H3N2, and B/Yamagata. Age group subanalyses of non-inferior immune responses to B/Victoria showed no clear trends (NI criteria were not met in any age subgroup).

Adults 50-64 years comprised 59.7% of the Efficacy Population and 66.0% of the Immunogenicity Population, driving results of the primary rVE analysis and immunogenicity endpoints, respectively. Because age subgroup analyses lacked statistical power, they do not allow definitive conclusions, but the trend towards lower efficacy and immune responses in older age groups is consistent with other studies of licensed influenza vaccines.

Subanalyses of efficacy and immunogenicity according to sex, race, and ethnicity demonstrated trends similar to the overall study population.

Among adults ≥50 years, subpopulation analyses of solicited AEs showed more frequent local injection site reactions in both Flublok RIV4 and IIV4 groups among females, whites, non-Hispanics, and younger subjects (50-64 years of age) as compared to males, non-whites, Hispanics, or older adults (≥65 years of age) [rates of any solicited local reaction 45.4%, 39.9%, 38.2%, and 53.0% versus 26.7%, 28.5%, 27.3%, and 40.8%, respectively]. Females reported slightly more systemic symptoms overall as compared to males (27.3% versus 21.8%), the largest difference being in the frequency of headache (14.6% vs 10.1%). All systemic symptoms were reported more frequently by younger adults as compared to adults ≥65 years of age [rates of at least one systemic symptom 29.0% vs 19.2%, respectively). The rates of solicited systemic symptoms between whites and non-whites and between Hispanics/Latinos and non-Hispanics/Latinos were similar. The numbers of subjects belonging to racial groups other than whites or blacks or of Hispanic/Latino ethnicity were too small for meaningful subanalyses.

Subanalyses of unsolicited AEs showed that females reported more AEs than males for most body system categories (Flublok RIV4 female vs male recipients 15.4% vs 11.7%; IIV4 female vs male recipients 16.0% vs 11.5%), but rates and severity grades were similar between treatment groups. Rates and severity grades of unsolicited AEs were similar both between whites and non-whites and treatment groups. Blacks/African Americans comprised the majority of non-white racial groups. Rates of unsolicited AEs among Hispanics/Latinos were slightly lower as compared to non-Hispanics/Latinos in both treatment groups (Flublok RIV4 Hispanic/Latino vs non-Hispanic/Latino 10.7% vs 14.0%; IIV4 Hispanic/Latino vs non-Hispanic/Latino 11.9% vs 14.3%) but severity grades

were similar. Age group subanalyses did not show large differences in the rates or severity of unsolicited AEs.

Subpopulation analyses of SAEs according to sex, race, and ethnicity revealed higher rates in whites as compared to blacks/African Americans (Flublok RIV4 2.6% vs 0.7%; IIV4 2.3% vs 0.6%, respectively) and in non-Hispanic/Latinos as compared to Hispanic/Latinos (Flublok RIV4 3.2% vs 0.1% vs IIV4 2.8% vs 0.3%, respectively). Overall, the rates were low and the significance of the observed trends was uncertain. No large differences were observed in the overall rate of SAEs between sexes or in the rates of death among any of the subpopulations.

Subpopulation analyses of MAES revealed trends towards more MAEs among females than males (Flublok RIV4 11.7% vs 6.2%; IIV4 11.9% vs 6.2%), whites than blacks/African Americans (Flublok RIV4 15.0% vs 2.6%; IIV4 15.5% vs 2.1%), and non-Hispanic/Latinos than Hispanic/Latinos (Flublok RIV4 17.2% vs 0.7%; IIV4 17.3% vs 0.8%). The largest imbalances were observed in the SOC categories of Infections and Infestations, Respiratory, Thoracic, and Mediastinal Disorders, and General Disorders and Administration Site Conditions, without notable imbalances for specific preferred terms, including influenza or ILI. The significance of these trends is uncertain.

2. Clinical and Regulatory Background

On January 16, 2013, Flublok was approved in adults 18 through 49 years of age for the active immunization of adults 18 years and older against disease caused by influenza subtypes A and type B contained in the vaccine. On October 29, 2014, the indication was extended to adults 50 years of age and older under accelerated approval regulations, based on acceptable safety and immunogenicity data, with a postmarketing requirement to conduct a study to confirm clinical benefit in this age group. Subsequent to approval, PSC began clinical development of a quadrivalent formulation with plans to transition manufacturing from Flublok to Flublok Quadrivalent once the latter is approved. In accordance with these plans, FDA agreed that the older adult and future pediatric PMRs could be conducted with the quadrivalent formulation.

2.1 Disease or Health-Related Condition(s) Studied

Influenza is an important infectious cause of death in the United States and throughout the world, with influenza-associated respiratory and circulatory mortality rates ranging from 3,349 to 48,614 in the U.S. from 1976 to 2007 (average annual mortality of 23,607) and 250,000 to 500,000 deaths worldwide each year. It is responsible for more deaths in the U.S. than all other vaccine-preventable diseases combined. In seasons when influenza A/H3N2 predominates, mortality has been 2.7 times higher than when other strains (A/H1N1 or B) have predominated. A Centers for Disease Control and Prevention (CDC) study covering the period 1990-1999, during which A/H3N2 predominated in the U.S., estimated an annual average mortality of 36,155. During seasonal influenza epidemics in the U.S. from 1979-2001, the CDC estimated that influenza-associated hospitalizations ranged from 55,000 to 431,000 per season. Complications, hospitalizations and deaths from seasonal influenza disproportionately affect persons ≥ 65 years, children < 5 years especially those < 2 years, and persons of any age with certain underlying cardiac, respiratory, metabolic, or immune compromising medical conditions. [5,7,8,9,10,11,13,14,31,33,85]

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 based on 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 18 variants of HA and 11 variants of NA, but only subtypes H1N1, H2N2, and H3N2 appear to circulate widely in humans. Influenza A has also been isolated from non-human species including birds, horses, and swine. In contrast to influenza A, influenza B is comprised of single HA and NA subtypes, and is only known to occur in humans. Antibodies to influenza surface antigens are subtype and strain-specific, and confer protection against future infection with identical strains, but not against another type or subtype. Historically, the A/H3N2 strain has been associated with a higher mortality rate as compared to the A/H1N1 or B strains, although the B strain is known to cause serious disease in children. [8,9,31,50,70]

Although influenza B viruses are not categorized into subtype based on HA and NA, they are divided into two distinct genetic lineages (Yamagata and Victoria) which have co-circulated since 1985 and comprise approximately 25% of positive influenza specimens in the U.S. Prior to the availability of quadrivalent influenza vaccines, which contain two B virus antigens derived from each of the two lineages, trivalent vaccines contained only one B virus antigen representing one lineage. During the ten seasons from 2001-2002 through 2010-2011, public health agencies were only able to correctly predict the predominant B lineage in five seasons, resulting in a mismatch between the vaccine and circulating strains for half of the 10 year period. The CDC estimated that in a season where there is a B strain mismatch, the availability of a quadrivalent vaccine could result in an annual reduction of 2,200-970,000 influenza cases, 14-8,200 hospitalizations, and 1-485 deaths. In recent years, rates of hospitalization and mortality attributed to influenza B virus have been recognized as being lower than A/H3N2 but higher than A/H1N1, and, overall, similar to those attributed to seasonal influenza A viruses. The CDC estimates that 80%-90% of seasonal influenza-related deaths and 50%-70% of hospitalizations occur in adults ≥65 years. Thus, the disease burden of influenza B infections in the elderly is substantial. Vaccine coverage of both B strains is also desirable in young children who experience the highest mortality due to B strains. Although influenza B causes ~25% of all clinical disease, 34% of the 309 pediatric deaths reported to the CDC during 2004-2008 and 38% of 115 pediatric deaths reported during the 2010-2011 season were due to influenza B. One case series of autopsies on patients with fatal influenza B infections (including 32 mostly healthy children <18 years) demonstrated that the influenza B infections were severe, rapidly progressive, and that 69% of 29 cases with available cardiac tissue were associated with myocardial injury. The authors also observed an age-related difference in complications of influenza B disease. While 82% of deaths in adults ≥18 years were associated with bacterial superinfection, most (90%) of the influenza B deaths in children <18 years were associated with myocardial injury. In 2013, the World Health Organization (WHO) and the VRBPAC recommended the inclusion of a second influenza B vaccine virus antigen in quadrivalent influenza vaccines to provide coverage of both B lineages. Since the NH 2013-2014 influenza season, five quadrivalent influenza vaccines have been licensed for use in the US. It is expected that, over time, quadrivalent formulations will become the standard of care for influenza vaccines. [4,11,13,50,70,75]

Since 1977, influenza A subtypes H1N1 and H3N2 and influenza B have co-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 annual change in the formulation of influenza vaccines for optimal protection. Neutralizing antibody 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 HI 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 influenza vaccines supports use of HI titers as a surrogate endpoint.[8,9,22,31,33,35,41]

The primary mode of controlling influenza disease is immunoprophylaxis. Because of the potential for serious and life-threatening influenza-related disease, the CDC's Advisory Committee on Immunization Practices (ACIP) has, over the last decade, broadened its recommendations for immunoprophylaxis of influenza and now recommends influenza vaccination for all persons 6 months of age and older without known contraindications. [8,11,14]

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Five licensed antiviral agents are available in the U.S. for the prevention or treatment of influenza in persons with confirmed or suspected severe, complicated, or progressive influenza, or in those at higher risk for complications. Treatment of persons without known risk factors may also be considered if treatment can be initiated within 48 hours of onset or if infection with a novel influenza virus is suspected. Two older adamantane agents, amantadine and rimantidine, are active only against influenza A and are no longer recommended because of widespread resistance since 2005. One of three neuraminidase (NA) inhibitors, oseltamivir is an oral antiviral indicated for the treatment of influenza A and B in persons ≥ 14 days of age and for chemoprophylaxis in persons ≥1 year of age. Frequent gastrointestinal side effects may limit its usefulness. Emergence of resistance during treatment with oseltamivir was a problem for seasonal H1N1viruses prior to their replacement by the 2009 pandemic H1N1 strains which are now in circulation and only rarely resistant. Currently, seasonal H3N2 and B strains are also rarely resistant to oseltamivir. Zanamivir, another NA inhibitor, is indicated for chemoprophylaxis of influenza in persons ≥ 5 years of age and for treatment in persons ≥ 7 years of age. It is administered as an orally inhaled powder and is associated with bronchospasm especially in persons with underlying asthma or chronic obstructive pulmonary disease. It is rarely associated with resistance. The third and newest NA inhibitor, peramivir, is a single dose intravenous antiviral indicated only for the treatment of uncomplicated influenza A and B viral infection in persons 18 years of age and older. Adverse events include diarrhea, serious cutaneous reactions and postmarketing reports of neuropsychiatric events. Due to concerns for potential emergence of resistance and side effects, NA inhibitors are considered important adjuncts but not substitutes for vaccination. [10,11,14,19,31]

2.3 Safety and Efficacy of Pharmacologically Related Products

In addition to Flublok, licensed influenza vaccines available in the United States (2015-2016 season) include: trivalent and quadrivalent inactivated influenza vaccines (IIV3 and IIV4), live-attenuated influenza vaccines (LAIV), and, more recently, one high dose and one adjuvanted trivalent inactivated vaccine. These vaccines are grown either in egg or cell culture. Six IIV3 (Afluria, Fluarix, FluLaval, Fluvirin, Fluzone, and Flucelvax)

and four IIV4 (Afluria, Fluarix, FluLaval, and Fluzone) standard dose (15 mcg HA per antigen) vaccines are licensed for use in the US in adults 18 years of age and older. A fourth IIV4 (Fluzone Quadrivalent Intradermal) is limited to use in adults 18-64 years of age. LAIV4 (FluMist Quadrivalent) 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 IIV3 has been estimated as 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 ≥ 65 years of age, or when there is a poor antigenic match between vaccine and circulating influenza virus strains. Because of lower immune responses observed in the elderly, two other trivalent inactivated influenza vaccines with improved immunogenicity over standard IIVs were developed and licensed for use in adults ≥65 years of age: Fluzone High Dose (45 mcg HA per antigen) and Fluad [the first U.S.-licensed IIV3 (Agriflu) formulated with an adjuvant (MF59)]. [8,12,13,14,15,16,18,20,21,25,31,33,40,44,45,55,56,57,60,63,64,65,69,72,73,81,86,92]

Seasonal inactivated influenza vaccines (IIV) licensed for use in the U.S. have a long history of safety. The most common adverse events (AEs) associated with IIVs are local injection site reactions, e.g., pain, erythema, and induration. These reactions generally occur in >10% of patients, are usually mild to moderate in intensity, and are relatively short in duration (24-48 hours). Systemic symptoms following vaccination, e.g., fever, arthralgia, myalgia, headache, are less common and, in randomized controlled trials, often occur at rates similar to those observed in placebo recipients making causality uncertain. [13,31,37,84,91]

Uncommon or rare AEs associated with influenza vaccines include neurologic events such as encephalitis, myelitis, and Guillain-Barre syndrome, and allergic or immediate hypersensitivity reactions, e.g., urticaria or angioedema. The incidence of anaphylaxis following IIV3 has been estimated as 1.35 cases per million doses (95% CI: 0.65, 2.47). [13,31,37,53,84,91]

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Flublok Quadrivalent has not been licensed by any other regulatory authority. However, Flublok trivalent influenza vaccine has been marketed in the US since its original approval in adults 18-49 years of age in January 2013 (STN 125285/0). Please see the Flublok PI and the clinical reviews of STN 125285 Amendments 0 and 78 for additional information regarding previous experience with Flublok in subjects 18-49 years and ≥50 years of age, respectively.

Currently, there are no other U.S.-licensed influenza vaccines manufactured in *Spodoptera frugiperda* (Sf) insect cells using 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.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

April 18, 2008: Original submission (OS) of BLA STN #125285/0 intended to support accelerated approval for Flublok. FDA issued two Complete Response (CR) letters (on

August 29, 2008 and January 10, 2010) due to manufacturing, clinical and statistical deficiencies. Please see the clinical review of the OS for details.

November 19, 2009: Because Flublok was a novel recombinant influenza vaccine produced by a new manufacturing process, the product was presented to the VRBPAC. Please see the clinical review of the OS for details.

Reviewer comment: The rates of hypersensitivity type events across studies did not reveal a large or clearly significant imbalance between Flublok and controls. However, the review team recognized that a larger safety database was needed to detect less common events.

August 8, 2012 and August 30, 2012 telecons: CBER informed PSC that we would consider traditional approval of Flublok in persons 18-49 years of age, but that approval in persons 50 years and older would require additional safety and effectiveness data. CBER informed PSC that: 1) accelerated approval would be considered in this age group based on GMT ratios for Flublok relative to Fluzone but not on SCR differences, and 2) traditional approval in adults 50 years and older would require a confirmatory clinical endpoint study in this population. In the August 30, 2012 telecon, the Applicant agreed to conduct a clinical endpoint study in persons 50 years and older to support traditional approval and address CBER's concerns that: 1) an HI titer correlating with protective immunity has not been established for BEVS-derived antigens; and 2) that these immunogenicity data would be bridged back to data from PSC04 that failed to meet the primary endpoint of vaccine efficacy (VE) against culture-confirmed CDC-ILI. Please see the clinical review of STN 125285/78 for additional discussion of these issues.

January 16, 2013: Flublok was granted traditional approval in adults 18 through 49 years of age based on the demonstration of effectiveness in prevention of culture-confirmed influenza illness and on an acceptable safety profile with an absence of clear safety signals in this population.

July 24, 2013: A pre-IND meeting was held for IND 15784, Flublok Quadrivalent. FDA provided advice regarding the design of a pediatric PMR, PSC08, in children and adolescents 6 through 17 years. We requested and PSC confirmed that egg-derived antigens would be used in the HI assay which would be performed by the (b) (4) . Please see the official meeting minutes for details.

October, 15, 2013: PSC submitted IND 15784 which included a two-phased protocol for PSC08 extending over two seasons. Due to deficiencies in the statistical analysis plan (SAP), PSC agreed to revise PSC08 to an independent exploratory phase 2 study and to submit a separate phase 3 protocol, PSC17, that would also be required to fulfill the pediatric PMR in children and adolescents 6 through 17 years.

October 23, 2013: PSC submitted an efficacy supplement, STN 125285/78, to support licensure of Flublok in persons ≥ 50 years of age. Please see the clinical review for additional information specific to this supplement.

October 29, 2013: PSC submitted an Initial Pediatric Study Plan (iPSP) for Flublok Quadrivalent to IND 15784/2.

August 18, 2014: PSC submitted IND 15784 Amendment 18 containing protocols PSC12 and PSC16. The Applicant had submitted earlier versions of these protocols to IND (b) (4) Amendments 65, 75, and 89, and IND 15784 Amendment 15 for our review. In accordance with our previous advice, the Applicant agreed that their proposed analysis of superior VE was exploratory and acknowledged that we would not include claims of superiority in the PI. PSC12 included plans to extend the study to a second season, if necessary, to accrue a sufficient number of cases for the primary analysis. The Applicant agreed to enroll adequate numbers of subjects in the age subgroups 50-64, 65-74, and ≥75 years of age to allow for subgroup analyses. PSC also agreed that HI titers in studies PSC12 and PSC16 would be measured by an HI assay using egg-derived antigens (IND 15784 Amendments 15 and 18).

October 29, 2014: CBER granted Flublok accelerated approval in adults 50 years of age and older based on acceptable safety and non-inferior GMT ratios as compared to U.S.-licensed Fluzone with a PMR to conduct a clinical endpoint study in this age group.

July 7, 2015 – September 11, 2015: In lieu of a pre-BLA meeting for submission of STN 125285/194, the Applicant requested advice via electronic mail regarding the format and Table of Contents of the submission. Please see summaries of CBER's advice to PSC on July 24, 2015, August 31, 2015, and September 11, 2105, available in the EDR under IND 15784.

March 9, 2016: The PeRC approved the final PSP for Flublok Quadrivalent.

March 22, 2016: PSC submitted a meeting request to discuss a revised pediatric plan in which they proposed replacing PSC14 and PSC17 with a single clinical endpoint study of the relative VE of Flublok Quadrivalent versus a U.S. and Mexican-licensed IIV4 comparator in children 3 through 17 years. The plan was acceptable to the review team. Please see the clinical review of IND 15974/54 and the meeting summary, available in the EDR, for details.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The lack of detailed SAE reports and inaccurate summary tables made the review of safety challenging and resulted in several information requests that delayed the review process.

Case narratives and documentation in the eCRF of deaths, SAEs and other AEs of interest, e.g., potential hypersensitivity events, lacked detail, which hindered review of AEs and assessments of attribution. Therefore, CBER requested additional information. In response to our request for additional details surrounding these events, the Applicant stated they were unable to provide details for the majority of events and stated "No information was provided regarding description of the evaluation including location, laboratory test results, imaging studies, or consultations". This included an SAE case narrative for one Flublok recipient (ID (b) (6)) for whom BiMO found the investigator had obtained hospital admission, discharge, and consultation notes and laboratory results. In another example, in response to our request to explain why details (that the reviewer found by going back to the original IND Safety Report) regarding the death of an IIV4 recipient (ID (b) (6)), including a Medical Examiner's Report, were omitted

from the case narrative, the Applicant stated that they did not feel it necessary to duplicate information that had previously been submitted to the IND.

Reviewer comment: It appeared that the Applicant was not meticulous in submitting a complete and accurate report that summarized SAEs and facilitated our review. This represents a limitation of the safety data. Nevertheless, for most of the reports, the reviewer was able to make a reasonable assessment of attribution based on the nature of the events (biological plausibility) and temporal relationship, and by searching the eCRFs and electronic datasets for details.

The Applicant pre-specified analyses of unsolicited adverse events occurring from Day 0 through Day 28. Although the Applicant's study reports and summary tables for both PSC12 and PSC16 indicated that the rates of unsolicited AEs occurred over this time period, review of the data revealed that the reported rates reflected incidence from Day 0 through Day 180. CBER requested that the Applicant submit corrected analyses.

The Applicant stated that they conducted a Per Protocol analysis on the immunogenicity population in PSC16 but did not provide the results in the CSR. When we requested these results, the Applicant responded that they actually had not performed the analysis but provided the analysis after we made a second request for the information. The Applicant also erroneously added a grade 4 event in the analysis of solicited local AEs for PSC16. The Applicant informed us of the error in the study report but submitted incorrect summary tables, necessitating a request for amended tables.

Reviewer comment: Overall, these issues did not rise to the level of a Refuse to File, Major Amendment, or Complete Response, and were resolved to the reviewer's satisfaction.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant stated that the protocols were written and conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization Consolidated Guideline for Good Clinical Practice E6 (ICH-GCP), federal regulations (21 CFR 50, 54, 56, and 312), and local ethical and regulatory requirements. These requirements included IRB approval of the protocol and the informed consent of human subjects.

Bioresearch Monitoring (BIMO), Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, conducted an inspection of two clinical study sites (51 and 54), where both PSC12 and PSC16 were conducted, and found no deficiencies that would preclude approval. Please see the BIMO review for details of the inspection.

3.3 Financial Disclosures

The Applicant signed an FDA Form 3454 and provided a list of investigators for the clinical studies submitted to this sBLA, certifying that they had not entered into any financial agreements with the investigators that could potentially influence the outcome of the study. The Applicant certified further that each listed investigator was required to disclose their financial interests and that no disclosable financial interests or arrangements as defined by 21CFR54.2 were reported.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

The Chemistry, Manufacturing, and Controls (CMC) review team did not identify any issues that would preclude licensure. Stability data for Flublok Quadrivalent supports a 6-month shelf life. Please see the CMC review for details of potency and stability issues.

4.2 Assay Validation

HI titers were determined by a validated assay that used egg-derived antigens supplied by (b) (4) . The statistical assay reviewer found that the HI assay validation data appeared to support its adequate performance against each of the four influenza antigens, including for the egg-derived B/Brisbane/60/2008 antigen, and was acceptable for its intended purpose in this supplement.

Reviewer comment: The HI assay and titers for PSC12 and PSC16 were performed by (b) (4) ***which uses whole virus in the assay. In previous studies of Flublok (PSC04, PSC03, and PSC06),*** (b) (4) ***performed the HI titer measurements and used rHA antigens in the assay. According to DVP, use of whole virus in the HI assay results in lower titers as compared to split virus or rHA as antigen.***

Reviewer comment: The immunogenicity data is discussed in this review within the following context:

- ***An HI correlate of protection (COP) has not been established for rHA vaccines even when egg-derived antigen is used in the HI assay; and***
- ***Use of egg-derived antigens in the HI assay to measure antibodies raised against rHA vaccines may result in lower titers against influenza B/Victoria viruses due to mutations (e.g., loss of a glycosylation site) that occur during egg adaptation and are documented to result in antigenic differences. This is also true for viruses of the B/Yamagata lineage.***

Given these uncertainties, in future studies of Flublok Quadrivalent, PSC might consider comparing results of HI titers using both egg- and rHA antigens in the assay and/or working to establish a COP for Flublok in a clinical endpoint study (e.g., the planned pediatric PMR PSC17). Please see Section 6.1.11.1 and the CMC/DVP review for further discussion of these issues.

4.3 Nonclinical Pharmacology/Toxicology

Not applicable. CBER did not require new non-clinical or toxicology data for this supplement because Flublok Quadrivalent is manufactured by the same process as Flublok and differs only in the additional B antigen.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vaccination with inactivated influenza vaccines induces antibody responses primarily against hemagglutinin (HA) and neuraminidase (NA). Strain-specific neutralizing antibodies against HA provide the main protection against infection and clinical disease. The anti-HA antibody response, measured by the hemagglutination inhibition (HI) assay, is currently the best available surrogate marker of activity that is reasonably likely to predict clinical benefit. Some studies (using egg-based vaccines) have shown that HI titers ranging from 1:32 to 1:40 are associated with protection from illness in approximately 50% of subjects and that protection from illness generally correlates with higher titers. However, prospective studies have not identified a specific HI titer that predicts protection against laboratory-confirmed influenza illness for either egg- or rHA-based vaccines. Other antibody, e.g., to NA, nuclear protein (NP), and/or M1 protein, and cellular responses to vaccination may contribute to protection.[8,9,22,29,31,33,35,41,58,73]

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

Please see the statistical review. When the clinical review was finalized, the statistical reviewer had identified no issues that would preclude approval of the supplement. At the statistician's request, the Applicant re-calculated immunogenicity and rVE endpoint analyses for PSC16 and PSC12, leading to minor revisions in these results (response to IR, STN 125285/194).

4.6 Pharmacovigilance

Please see the OBE/DE review of the Pharmacovigilance Plan (PVP) and Section 11.6. The OBE/DE reviewer identified no safety concerns that would require a postmarketing study (PMR) designed specifically to evaluate a safety endpoint, and did not recommend a risk evaluation and mitigation strategy (REMS) as necessary for Flublok Quadrivalent. A large postmarketing safety study of the trivalent formulation of Flublok (PSC13) was a PMC agreed to at the time of the original approval and is expected to be completed by 2016-2017. Unless new data (e.g., from PSC13 or routine postmarketing surveillance) raise concerns for a safety signal, OBE/DE does not plan to recommend another postmarketing safety study for the quadrivalent formulation. A pregnancy registry (PSC15) will be established for recipients of both Flublok (trivalent) and Flublok Quadrivalent.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

PSC submitted two studies, PSC16 and PSC12, to support licensure of Flublok Quadrivalent in adults 18-49 and ≥50 years, respectively. These studies were reviewed individually in Section 6. The reviewer chose not to request integrated analyses (Sections 7 and 8) because the two age populations have different immune responses

and safety profiles, and because of different study designs for the primary endpoint (immunogenicity versus clinical efficacy). The reviewer evaluated the study data for consistency with information included in the proposed PI. CBER and PSC had agreed that non-inferior immune responses elicited by Flublok Quadrivalent as compared to IIV4 were adequate to infer clinical benefit based on the clinical endpoint data that supported licensure of Flublok (trivalent) in adults 18-49 years while PSC12 independently demonstrated clinical benefit in adults ≥50 years. Because the vaccines are manufactured by the same process and have overlapping compositions, clinical efficacy and safety data for Flublok (trivalent) were considered relevant to Flublok Quadrivalent and were included in the proposed Flublok Quadrivalent PI. Conversely, because PSC12 fulfilled the PMR associated with accelerated approval of Flublok (trivalent) in adults ≥50 years, the Flublok (trivalent) PI was updated with clinical efficacy data from the quadrivalent study PSC12.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- STN 125285/197 Modules 1, 2 and 5, and datasets associated with PSC12 CSR and PSC16 CSR (Module 5).
- STN 125285/194.1 – Response to January 22, 2016 IR (PSC16 AESIs and PVP)
- STN 125285/194.2 – Response to January 20, 2016 IR (PPP for PSC16, Gr 4 solicited tenderness, Day 28 TEAEs).
- STN 125285/194.3 – Response to January 11, 2016 IR – Solic AE duration, SAE narratives, AE discontinuations.
- STN 125285/194.4 – Response to February 6, 2016 IR. Request for PSC16 PPP analysis and clarification of additional error in solicited AE results table.
- STN 125285/194.6 – Response to February 18, 2016 IR – PSC12 SAE narrative discrepancy for a subject who died of cocaine overdose. Request for detailed numbers of confirmed ILIs by type and test method.
- STN 125285/194.9 – Response to March 1, 2016 Statistical IR, revised efficacy and immunogenicity tables for PSC16 and PSC12.
- STN 125285/194.19 – Response to May 20, 2016 Statistical IR, immunogenicity subset.
- STN 125285/194.20 – Response to June 8, 2016 IR, antigenic characterization.
- STN 125285/194.22 – Response to June 27, 2016 IR, pregnancies in PSC16.
- STN 125285/194.28 – Response to August 10, 2016 IR regarding pregnancy registry (to include recipients of trivalent and/or quadrivalent formulations).
- STN 125285/194.26, 33, and 35 – Labeling negotiations.

5.3 Table of Studies/Clinical Trials

Table 5 presents the characteristics of the two clinical studies submitted to support licensure of Flublok Quadrivalent in adults 18 years and older.

Table 5: Summary of Clinical Trials Submitted to STN 125285/194

Study ID NCT# Season Location	Design	Population Enrolled/ Randomized	Objectives	Endpoints*	Analysis Populations
PSC16 NCT 02290509 NH 2014-2015 USA	Phase 3, observer-blind, comparator-controlled, multicenter trial, randomized 3:1 to receive a single 0.5mL IM dose of Flublok RIV4 (45mcg HA per strain) or IIV4 (Fluarix RIV4) (15 mcg HA per strain)	Healthy adults 18 through 49 years 1350 total 1011 Flublok 339 IIV4	Non-inferior immunogenicity Safety	Co-primary: GMT ratio and SCR difference for each strain. Secondary: Frequency and severity of solicited AEs (reactogenicity) (7 days), unsolicited AEs (28 days), and SAEs/MAEs (180 days). SCRs, % HI titer ≥1:40	Safety: 1330 total 998 Flublok 332 IIV4 Immunogenicity: 1292 total 969 Flublok 323 IIV4
PSC12 NCT 02285998 NH 2014-2015 USA	Phase 3, observer-blind, comparator-controlled, multicenter trial, randomized 1:1 to receive a single 0.5mL IM dose of Flublok RIV4 (45mcg HA per strain) or IIV4 (Fluarix RIV4) (15 mcg HA per strain)	Medically stable adults ≥50 years 8963 total** 4474 Flublok 4489 IIV4	Primary: Non-inferior vaccine efficacy Secondary: Non-inferior immunogenicity Safety	Primary: rt-PCR-confirmed, protocol-defined ILI caused by any influenza strain that began at least 14 days post-vaccination through the EOIS Secondary: rt-PCR-confirmed, CDC-defined ILI, any strain; Culture-confirmed, protocol-defined ILI, matched strains; Culture-confirmed, CDC-defined ILI, matched strains. GMT ratio and SCR difference for each strain. Frequency and severity of solicited AEs (reactogenicity) (7 days), unsolicited AEs (28 days), and SAEs/MAEs (180 days).	Safety: 8672 total 4328 Flublok 4344 IIV4 Efficacy: 8604 total 4303 Flublok 4301 IIV4 Immunogenicity: 617 total 317 Flublok 300 IIV4

Source: STN 125285/194, Module 5, PSC16 CSR text and Table 14.1.1; PSC12 CSR text and Table 14.1.1.
Abbreviations: NCT=National Clinical Trials identifier; NH=Northern Hemisphere; IM=intramuscular; RIV4=quadrivalent recombinant influenza vaccine; IIV4=quadrivalent inactivated influenza vaccine; HA=hemagglutinin; GMT=geometric mean titer; SCR=seroconversion rate; HI=hemagglutination inhibition; ILI=influenza-like illness; EOIS=end of influenza season; rt-PCR=reverse transcriptase polymerase chain reaction; CDC=Centers for Disease Control and Prevention; AE=adverse event; SAE=serious adverse event; MAE=medically=attended adverse event.
*Immunogenicity endpoints were assessed at 28 days post-vaccination.
**Of 9003 subjects enrolled and randomized, 8988 received a dose of study vaccine. Fifteen subjects withdrew prior to vaccination and were not included in any analyses. Per PSC's report, Randomized Population (n=8963) excludes 40 randomized subjects who either withdrew prior to vaccination (n=15) or for whom the vaccine received could not be verified (n=25; 12 assigned to Flublok RIV4; 13 assigned to IIV4).

5.4 Consultations

Not applicable.

5.4.1 Advisory Committee Meeting

Not applicable.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 – PSC16

"Double-Blind, Randomized, Active-Controlled Comparison of the Immunogenicity and Safety of Flublok Quadrivalent versus IIV4 in Healthy, Medically Stable Adults 18-49 Years of Age". NCT#: 02290509.

6.1.1 Objectives

Primary Objective

To demonstrate non-inferior immunogenicity of the four antigens in the Flublok RIV4 formulation to the corresponding antigens in the licensed IIV4 through evaluation of:

- The ratio of post-vaccination hemagglutination inhibition (HI) geometric mean titers (GMTs) for each of the four antigens, and
- The difference in HI seroconversion rates (SCRs) to each of the four antigens.

Secondary Objectives

- To evaluate the SCRs and proportion of subjects with post-vaccination HI titers ≥1:40 (% HI≥1:40) for each of the four antigens contained in Flublok RIV4.
- To evaluate the safety and reactogenicity of Flublok RIV4 in adults 18-49 years.

6.1.2 Design Overview

PSC16 was a Phase 3, observer-blind, randomized, comparator-controlled, multicenter trial designed to evaluate the safety, reactogenicity, and immunogenicity of Flublok RIV4 as compared to a U.S.-licensed IIV4 in ambulatory, medically stable adults 18-49 years of age. A total of 1350 subjects were enrolled and randomized 3:1 to receive either Flublok RIV4 or IIV4. Serum HI titers were collected prior to vaccinations on Day 0 and again on Day 28. The immunogenicity of the four antigens present in Flublok RIV4 were compared to the corresponding antigens in IIV4 using the CBER-defined criteria of Day 28 post-vaccination HI GMT ratios and SCR differences (8 co-primary endpoints) to establish non-inferiority. Solicited local and systemic reactogenicity events were actively monitored for 7 days, unsolicited adverse events (AEs) for 28 days, and serious adverse events (SAEs) and medically-attended events (MAEs) for 6 months post-vaccination.

Reviewer comment: PSC submitted a protocol synopsis for PSC16 with questions for CBER to IND 15784 Amendment 15. We responded to the Applicant's request for feedback in a July 1, 2014 advice and information (AI) request letter. We subsequently agreed to the protocol, SAP and revisions, submitted to IND 15784 Amendments 18, 21 and 22, in which the Applicant incorporated our previous recommendations and requests (e.g., regarding use of a U.S.-licensed comparator, primary endpoints, duration of safety monitoring, and halting criteria). The study design, randomization and blinding procedures were deemed adequate by the statistical reviewer.

6.1.3 Population

Selected Inclusion Criteria:

- Ambulatory adults 18 through 49 years, in good health or medically stable.
- Non-pregnant (negative test within 24 hours of vaccination), non-breastfeeding females.
- No receipt of influenza vaccines within 180 days or plans to receive influenza or other vaccines (licensed or investigational) during the study.

Selected Exclusion Criteria:

- Prior serious or severe reaction to influenza vaccine.
- Known contraindication to study vaccines (as described in the package inserts).
- Receipt of new diagnosis, medications (licensed or investigational), or vaccines within 30 days of enrollment.
- Immunocompromising conditions or interventions that might adversely affect the immune response.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Flublok RIV4 contained a total of 180mcg recombinant hemagglutinin (rHA), 45mcg per each of four antigens derived from influenza A/H1N1, A/H3N2, B Yamagata, and B Victoria viruses, in a total volume of 0.5mL, provided in pre-filled syringes. The antigens were stored in a sodium phosphate buffer with 0.005% Tween-20. rHA content was determined by the single radial immunodiffusion assay (SRID). Batch #QFCA1401.

U.S.-licensed IIV4 (Fluarix Quadrivalent) contained a total of 60mcg of influenza hemagglutinin (HA), 15 mcg per each of four antigens derived from influenza A/H1N1, A/H3N2, B Yamagata, and B Victoria viruses, in a total volume of 0.5mL, provided in pre-filled syringes. Lot#GA22N.

Each study vaccine contained antigens derived from the four influenza strains (or "like viruses") recommended by the VRBPAC for inclusion in quadrivalent vaccines for the NH 2014-2015 season (shown in Table 6):

Table 6: Influenza Virus Strains Included in the Study Vaccines – PSC16

Strain	Flublok RIV4	Fluarix QIV
A/H1N1	A/California/07/2009	A/Christchurch/16/2010*
A/H3N2	A/Texas/50/2012	A/Texas/50/2012
B/Yamagata lineage	B/Massachusetts/2/2012	B/Massachusetts/2/2012
B/Victoria lineage	B/Brisbane/60/2008	B/Brisbane/60/2008

Source: Adapted from STN 125285/194, Module 5, CSR PSC16, pp.27-28.
*An influenza A/California/07/2009-like virus

Each subject received a single 0.5mL dose of assigned study vaccine administered intramuscularly (IM) in the deltoid region of the upper arm.

6.1.5 Directions for Use

Not applicable.

6.1.6 Sites and Centers

Table 7 presents a list of each study site, principal investigator, and number of subjects.

Table 7: Study Sites, Investigators, and Subjects* - PSC16

Site	Investigator	Location	#Subjects*
50	George Bauer, MD	Metairie, LA	133
51	Paul Bradley, MD	Savannah, GA	148
52	James Cervantes, MD	Bellevue, NE	123
53	Laurence Chu, MD	Austin, TX	135
54	William Douglas, MD	Sacramento, CA	143
55	David Ensz, MD	Dakota Dunes, SD	125
56	Brandon Essink, MD	Omaha, NE	119
57	Terry Poling, MD	Wichita, KS	148
58	Jeffrey Rosen, MD	Coral Gables, FL	123
59	William Seger, MD	Fort Worth, TX	133

Source: Adapted from STN 125285.194, PSC16 CSR, Appendix 16.1.4 and electronic datasets.
*Number of subjects in the Safety Population

6.1.7 Surveillance/Monitoring

Table 8 presents the schedule of procedures for Study PSC16.

Table 8: Study Procedures – PSC16

Visit	**1**	**2[1]**	**3**	**4[1]**	**Early Exit[1]**
Day (window)	**0**	**7 (7-9)**	**28 (26-35)**	**180 (160-200)**	**--**
Informed consent	X	--	--	--	--
Eligibility criteria	X	--	--	--	--
Medical history	X	--	X	--	X
Targeted physical exam[2]	X	--	--	--	X
Urine pregnancy test[3]	X	--	--	--	--
Oral temperature	X	--	--	--	--
Serum HI titer	X	--	X	--	--
Vaccination	X	--	--	--	--
Post-vaccination observation (30 min)	X	--	--	--	--
Distribute/instructions on use of ruler, thermometer, and Memory Aids	X	--	--	--	--
Solicited AE (Memory Aid A) review[4]	--	X	--	--	--
Unsolicited AE (Memory Aid B) review[5]	--	X	X[1]	--	--
Memory Aid A[4] and B[5] collection	--	--	X	X	X
SAE and MAE review[6]	X	X	X	X	X
Concomitant medications review	X	X	X	--	X

Source: Adapted from STN 125285/194, Module 5, PSC16 CSR, Table 9.
[1]Assessed remotely via phone call, email, text message or other electronic means.
[2]Includes vital signs, pharynx, skin, mucous membranes, cervical and axillary lymph nodes, lungs, heart, and extremities.
[3]For women of child-bearing potential, a negative pregnancy test must be documented within 24 hours prior to vaccination.
[4]Memory Aid A – To record solicited AEs from Days 0-7. Reviewed via phone contact on Day 7, returned to study site on Day 28.

[5]Memory Aid B – To record all unsolicited AEs from Days 0-28. Reviewed on Days 7 and 28. Returned to the study site by the end of the study.
[6]Subjects instructed to call study site as soon as possible to report an SAE.

After collection of baseline HI serologies on Day 0, subjects received a single 0.5mL IM dose of study vaccine. Subjects recorded solicited AEs (actively collected) on Memory Aid A from Day 0 through Day 7 and all unsolicited AEs (passively collected) from Day 0 through Day 28 on Memory Aid B. Subjects returned to the study site on Day 28 for post-vaccination HI titers, review of AEs, and collection of Memory Aid A. Safety follow-up was otherwise conducted via telephone or other electronic means as outlined in Table 8.

Definitions and Criteria for the Assessment of Severity and Causality of AEs
Definitions of AEs and SAEs were consistent with those in 21 CFR 312.32. Unsolicited AEs were defined as starting or worsening after vaccination (treatment-emergent). AEs were followed to resolution or stabilization. MAEs were defined as adverse events leading to a visit to or from medical personnel for any reason, including emergency department (ED) visits. Telephone contact with a healthcare professional was not considered an MAE. If an MAE met SAE criteria, it was also reported as an SAE.

Solicited local and systemic AEs and the scale for grading the severity of these events are presented in Table 9:

Table 9: Toxicity Grading Scale for Solicited Local and Systemic Reactogenicity – PSC16

Injection site Reaction	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hrs or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Does not interfere with activity	Discomfort on movement	Discomfort at rest or required prescription medication	ER visit or hospitalization
Erythema/Redness	25 to ≤50mm Small	51 to ≤100mm Medium	>100mm Large	Necrosis or exfoliative dermatitis
Induration/Firmness*	25 to ≤50mm Small	51 to ≤100mm Medium	>100mm Large	Necrosis
Systemic Reactogenicity	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Shivering/Chills Fatigue Myalgia/Muscle ache Joint ache Headache Nausea	No interference with activity	Some interference with activity, or, for headache, repeated use of non-narcotic pain reliever >24 hrs.	Significant interference/prevents daily activity or requires prescription meds, or, for headache, any use of narcotic pain reliever.	ER visit or hospitalization
Body temperature	100.4-101.1°F	101.2-102.0°F	102.1-104.0°F	>104.0°F

Source: Adapted from STN 125285/194, Module 5, Volume 1, PSC16 Protocol, pp.34-35.
*Induration/Firmness was changed to Firmness/Swelling on the subject diary card and eCRF.

Reviewer comment: Solicited AEs were similar to those collected in previous clinical studies of Flublok, and were events commonly reported in other adult influenza vaccine trials.

The toxicity grading scale for unsolicited AEs is presented in Table 10:

Table 10: Toxicity Grading Scale for Unsolicited Adverse Events – PSC16

Grade	Definition
Grade 1 (Mild)	No interference with activity
Grade 2 (Moderate)	Some interference with activity not requiring medical intervention
Grade 3 (Severe)	Prevents daily activity and requires medical intervention
Grade 4 (Life-threatening)	ED visit or hospitalization

Source: Adapted from STN 125285/194, Module 5, Volume 1, PSC16 Protocol, p.33-34.

Criteria for the Assessment of Causality of Unsolicited AEs

- Not related: Events were clearly considered due to extraneous causes (e.g., pre-existing or known medical condition, concomitant medication, environmental factor, etc.) unrelated to a study product. It can be readily explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
- Related: All AEs were considered related if they were not assessed as non-related.

Halting Criteria and Data Monitoring Committee (DMC)

The study was to halt if:

- The incidence of Grade 3 (severe) or worse reactogenicity notably exceeded the expected incidence based on the study vaccine PIs, or
- Three or more SAEs of the same type were assessed as unexpected and related to study vaccine.

An independent DMC was responsible for reviewing any AEs that triggered halting rules.

6.1.8 Endpoints and Criteria for Study Success

Co-Primary Endpoints

The study had eight co-primary immunogenicity endpoints:

- HI GMT at post-vaccination Day 28 for each of the four vaccine antigens in each treatment group
- SCRs at post-vaccination Day 28 for each of the four vaccine antigens in each treatment group

Seroconversion was defined as either a pre-vaccination HI titer of < 1:10 and a post-vaccination HI titer of ≥ 1:40, or a pre-vaccination HI titer of ≥ 1:10 and a minimum 4-fold rise in post-vaccination HI titer at Day 28.

The pre-specified success criteria for establishing the non-inferior immunogenicity of Flublok RIV4 as compared to IIV4 were as follows for all four vaccine antigens:

- UB of the 2-sided 95% CI for the GMT_{IIV4} / $GMT_{Flublok\ RIV4}$ ≤ 1.5, *AND*
- UB of the 2-sided 95% CI for the SCR_{IIV4} – $SCR_{Flublok\ RIV4}$ ≤ 10%.

Review comment: The study endpoints and success criteria were pre-specified and agreed upon with CBER.

Secondary Endpoints

- SCRs at post-vaccination Day 28 for all four antigens in each treatment group.

- Proportion of subjects with HI titers ≥ 1:40 (% ≥ 1:40) at post-vaccination Day 28 for all four antigens in each treatment group.
- Success criteria for the immune response endpoints:
  - The LB of the 2-sided 95% CI for the SCR must be ≥ 40%, *AND*
  - The LB of the 2-sided 95% CI for the % ≥ 1:40 must be ≥ 70%.
- Incidence and severity of solicited local and systemic reactogenicity events reported via the Memory Aid during Days 0-7 following vaccination.
- SAEs and other unsolicited AEs and MAEs occurring during the 28 days following vaccination.
- SAEs and MAEs occurring up to 6 months post-vaccination.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please see the statistical review for a complete discussion of the statistical analysis plan.

Hypothesis
For the co-primary endpoint of GMT ratios, the null and alternative hypotheses were, for each of the four corresponding antigens included in the study vaccines:
H_0: $GMT_{IIV4} / GMT_{Flublok\ RIV4} \geq 1.5$,
H_A: $GMT_{IIV4} / GMT_{Flublok\ RIV4} < 1.5$
Where 1.5 represents the non-inferiority margin.

For the co-primary endpoint of SCR differences, the null and alternative hypotheses were, for each of the four corresponding antigens included in the study vaccines:
H_0: $SCR_{IIV4} - SCR_{Flublok} \geq 10\%$
H_A: $SCR_{IIV4} - SCR_{Flublok} < 10\%$
Where 10% represents the non-inferiority margin.

Study Endpoints – Please see Section 6.1.8 and specific solicited AE parameters defined in Section 6.1.7. Adverse events were coded using the Medical Dictionary for Regulatory Activites (MedDRA) version 15.1.

- Safety data was summarized using descriptive statistics. Unsolicited AEs were summarized by MedDRA system organ class (SOC) and preferred term (PT) for each vaccine treatment group. For each subject, the greatest severity within each category (overall, SOC, or PT) was summarized. Subjects were counted only once per PT, SOC, maximum severity, and closest relationship to study vaccine.

Sample Size
The sample size required to demonstrate a non-inferior difference in SCRs assuming a NI margin of 10%, one-sided alpha level of 0.025, and 70% SCR for the IIV4 group, with 80% power was 330 subjects per treatment group. The sample size required to demonstrate non-inferior GMT ratios assuming a NI margin of 1.5, one-sided alpha level of 0.025, and a coefficient of variation of 0.53, with 80% power was 128 subjects per treatment group. Because successfully meeting all eight co-primary endpoints was required to demonstrate non-inferiority, no adjustment in alpha for multiplicity was necessary. No interim analyses were conducted.

Blinding: Subjects and study staff, with the exception of designated staff who administered the vaccine, were blinded to treatment.

Missing data: Missing data was not imputed. Rates of solicited reactogenicity events were calculated using the denominator of the number of subjects in each treatment group with at least one recorded data point during the 7-day post-vaccination surveillance period for each solicited AE parameter. The sponsor conducted sensitivity analyses for solicited AEs imputing a severity of Grade 3 (severe) for missing severity data.

Changes in Study Conduct or Planned Analyses – The sponsor made no changes to the final protocol or SAP.

6.1.10 Study Population and Disposition

The first subject was enrolled on October 22, 2014. The last subject completed the study on May 14, 2015.

6.1.10.1 Populations Enrolled/Analyzed

Immunogenicity Population (IP)
The IP was the primary immunogenicity analysis population and included all randomized subjects who received a dose of study vaccine, provided serum samples for Day 0 and Day 28 HI titers within specified windows, and subjects had no major protocol deviations that might adversely impact the immune response.

Per Protocol Population (PPP)
The Applicant stated that a PPP analysis was conducted on subjects with no missing data or protocol deviations as a sensitivity analysis to the IP.

Safety Population (SP)
The SP included all randomized subjects who received a dose of study vaccine and from whom any evaluable safety data were available after administration.

Reactogenicity Population (RP)
The RP included all randomized subjects who received study vaccine and who provided reactogenicity data on Memory Aid A on at least one occasion during the 7 days after vaccination. The RP was subdivided into three categories based on the type of reactogenicity data reported: A) injection site reactions; B) systemic reactions; and C) body temperature.

Subjects were analyzed according to treatment received.

6.1.10.1.1 Demographics
Table 11 presents demographics and baseline characteristics of the Safety Population according to treatment group. Distribution of characteristics across treatment groups was generally balanced. The mean age of subjects was 33.3 years in the Flublok RIV4 group and 34.0 years for IIV4. Females, white/Caucasians, and non-Hispanics comprised the majority of subjects in the study population (64.7%, 59.4%, and 83.5%, respectively).

Table 11: Demographics and Baseline Characteristics – PSC16 (Safety Population)

Characteristic	**Flublok RIV4 N=998**	**IIV4 N=332**	**U.S. Census (July 2014)***
Mean Age (yrs)	33.3	34.0	--

Characteristic	Flublok RIV4 N=998	IIV4 N=332	U.S. Census (July 2014)*
Median Age (yrs)	33.0	34.0	--
Min, Max Age (yrs)	18, 50	18, 49	--
Gender – Male, %	36.0	33.1	49.2%
Gender – Female, %	64.0	66.9	50.8%
Race, %	--	--	--
American Indian/Alaska Native	0.7	0.9	1.2%
Asian	0.3	1.2	5.4%
Black/African American	37.7	34.3	13.2%
Native Hawaiian/Pacific Islander	1.1	0.6	0.2%
White/Caucasian	59.0	60.8	77.4%
Other	1.2	2.1	--
Ethnicity, %	--	--	--
Hispanic/Latino	16.2	17.2	17.4%
Non-Hispanic/Latino	83.8	82.8	82.6%

Source: STN 125285/194, Module 5, PSC16 CSR, Table 14.1.3
*U.S. census data as of July 1, 2014 accessed on February 29, 2016 at http://www.census.gov/popest/data/
Total U.S. population=318,857,056. Adults 18-64 yrs=199,030,227. Adults ≥65 yrs=46,243,211. Male=156,936,487. Female=161,920,569. White=246,660,710. Black/African American=42,158,238. American Indian/Alaskan Native=3,960,971, Asian=17,339,053. Native Hawaiian/Pacific Islander=741,601. ≥two races=7,996,483. Non-Hispanic/Latino=263,469,517. Hispanic/Latino=55,387,539.

Reviewer comment: Males and Asians were underrepresented while females and Blacks/African Americans were overrepresented relative to the total U.S. population.

Reviewer comment: Prior season influenza vaccination history was not collected in this study.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Medical History

The most common pre-existing conditions among all subjects in the Safety Population belonged to the following categories of disorders: allergies (24.2%), genital/reproductive tract (22.9%), psychiatric (15.0%), HEENT (14.4%), musculoskeletal (13.2%), gastrointestinal tract (12.1%), cardiovascular (11.4%), nervous system (8.4%), and metabolic/endocrine (7.8%).

Reviewer comment: The electronic datasets were evaluated for subjects' medical history. Past and ongoing medical conditions consisted of disorders commonly found in a young adult population and appeared balanced between treatment groups. Four subjects in the Flublok RIV4 group (and none in the IIV4 group) had previous allergic reactions to bee stings or insect bites, but had no anaphylaxis or allergic reaction to the study vaccine. No subject had a known history of an immune disorder that would have negatively impacted the immune response to study vaccines or that led to exclusion from the Immunogenicity Population.

Concomitant Medications

A total of 51.1% of subjects in the Safety Population (Flublok RIV4 50.3%; IIV4 53.6%) reported taking concomitant medications at enrollment and/or during the study. Steroid use was primarily topical or inhaled in accordance with the protocol. One subject (Flublok RIV4 recipient) had a history of intermittent steroid injections as needed for low

back pain since 2012. Another Flublok recipient received one dose of dexamethasone for "cold, sore throat" on study Day 6. A third Flublok recipient had been receiving daily injections of glatiramer acetate for multiple sclerosis for years prior to enrollment. No other significant systemic steroid use or potentially immunosuppressive therapy was identified in evaluation of the sponsor's tables, listings, or electronic datasets. A total of 36 subjects, 27 (2.7%) Flublok RIV4 and 9 (2.8%) IIV4 recipients, were taking HMG CoA reductase inhibitors (statins) for hypercholesterolemia at the time of vaccination and for the duration of the study.

Reviewer comment: Overall, medication use was balanced between treatment groups and included medications typical for a younger adult population, e.g., medications for birth control, headaches, pain, asthma/seasonal allergies, hypertension, and anxiety/depression. No significant or disproportionate use of agents that might adversely affect immune responses was identified. Although recent observational studies have suggested that statins may lower the effectiveness of influenza vaccines through their immunomodulatory effects, this association requires further evaluation and including whether it applies to all influenza vaccines. The use of statins in this study was low overall, balanced between treatment groups, and unlikely to have significantly influenced the interpretation of study results. [2,6]

6.1.10.1.3 Subject Disposition

All 1350 subjects enrolled and randomized received a dose of study vaccine. Table 12 presents the disposition of subjects and analysis populations for PSC16.

Table 12: Subject Disposition and Analysis Populations, All Subjects Enrolled and Randomized – PSC16

Disposition	Flublok RIV4 N=1011 n(%)	IIV4 N=339 n(%)
Randomized Population	1011	339
Immunogenicity Population	969 (95.8)	323 (95.3)
Safety Population	998 (98.7)	332 (97.9)
Reactogenicity Population	996 (98.5)	332 (97.9)
-Reactogenicity Population A[1]	996 (98.5)	332 (97.9)
-Reactogenicity Population B[2]	994 (98.3)	332 (97.9)
-Reactogenicity Population C[3]	990 (97.9)	327 (96.5)
Completed Study	962 (95.2)	325 (95.9)
Primary Reason for Early Withdrawal	--	--
-adverse event	0	0
-investigator decision	0	0
-lost to follow-up	38 (3.8)	11 (3.2)
-sponsor request	0	0
-withdrawal of consent unrelated to AE	9 (0.9)	2 (0.6)
-other	2 (0.2)	1 (0.3)
Subjects who returned Memory Aid A	934 (92.4)	314 (92.6)
Subjects who returned Memory Aid B	877 (86.7)	288 (85.0)

Source: STN 125285/194, Module 5, PSC16 CSR Tables 12 and 14.1.1
[1]Subjects who recorded any injection site reactogenicity data in Memory Aid A, Days 0-7.
[2]Subjects who recorded any systemic reactogenicity data in Memory Aid A, Days 0-7.
[3]Subjects who recorded any body temperature data in Memory Aid A, Days 0-7.

Reviewer comment: Subject disposition was balanced between treatment groups including the proportion of subjects who completed the study (Flublok RIV4 95.2%, IIV4 95.9%). The early withdrawal rate, primarily due to lost to follow-up (Flublok RIV4 3.9%, IIV4 3.2%) was low. No subject withdrew due to an AE. Compliance with returning Memory Aid A to the study site on Day 28 was good (92.4%-92.6%) while returning Memory Aid B via mail was lower (85.0%-86.7%). Evaluation of the electronic datasets was consistent with the sponsor's report.

Major protocol deviations that excluded subjects in the Randomized Population from the immunogenicity analyses are summarized in Table 13.

Table 13: Protocol Deviations – PSC16 (Randomized Population)

Deviation Category	Flublok RIV4 N=1011 n(%)	IIV4 N=339 n(%)
Subjects with any major protocol deviation[1]	20 (2.0)	15 (4.4)
-Dosing error	1 (0.1)	2 (0.6)
-Exclusion criteria	1 (0.1)	0
-Lab sample missing or invalid	5 (0.5)	5 (1.5)
-Missed study visit	14 (1.4)	11 (3.2)
-Procedure not per protocol	2 (0.2)	1 (0.3)
-Other	1 (0.1)	1 (0.3)

Source: STN 125285/194, PSC16 CSR, Module 5, Table 14.1.2.2.
[1]Excluded from Immunogenicity Populations

Reviewer comment: The proportion of subjects with major protocol deviations leading to exclusion from the immunogenicity analyses in the IIV4 group (4.4%) was approximately twice as high as in the Flublok RIV4 group (2.0%). Most deviations were due to missing the study visit at which serology samples were to be collected. However, rates of missing laboratory samples were generally low in both groups (IIV4 1.5%, Flublok RIV4 0.5%), and was unlikely to significantly influence the interpretation of study results.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Table 14 presents the co-primary endpoint results of baseline HI GMTs and Day 28 post-vaccination GMTs and GMT ratios of IIV4 relative to Flublok RIV4 for each vaccine antigen (Immunogenicity Population).

Table 14: Baseline and Day 28 Post-Vaccination HI GMTs and GMT Ratios for Flublok Quadrivalent Relative to IIV4 in Adults 18 through 49 Years of Age – PSC16 (Immunogenicity Population)

Strain	Day	RIV4 GMT (95% CI) N=969	IIV4 GMT (95% CI) N=323	GMT Ratio (95% CI)	Met GMT NI Criteria?*
A/H1N1	0	59 (54,65)	53 (45,63)	--	--
A/H1N1	28	493 (460,527)	397 (358,441)	0.81 (0.71,0.92)	Yes
A/H3N2	0	74 (68,82)	70 (60,81)	--	--

Strain	Day	RIV4 GMT (95% CI) N=969	IIV4 GMT (95% CI) N=323	GMT Ratio (95% CI)	Met GMT NI Criteria?*
A/H3N2	28	748 (700,800)	377 (341,417)	0.50 (0.44,0.57)	Yes
B/Yamagata	0	26 (24,29)	24 (21,28)	--	--
B /Yamagata	28	156 (145,168)	134 (119,151)	0.86 (0.74,0.99)	Yes
B/Victoria	0	12 (11,13)	11 (10,12)	--	--
B/Victoria	28	43 (40,46)	64 (57,71)	1.49 (1.29,1.71)	No

Source: STN 125285/194.9, Module 5, PSC16 CSR, Table 14.2.1.1.1 (07Mar2016).
Abbreviations: HI=hemagglutinin inhibition; RIV4=Flublok Quadrivalent; IIV4=Fluarix Quadrivalent; GMT=geometric mean titer.
*Success criteria for the GMT ratio (GMT_{IIV4} / GMT_{RIV4}): UB of the 95% CI must be ≤ 1.5.

Flublok RIV4 met pre-specified success criteria for non-inferior post-vaccination GMTs relative to IIV4 for both influenza A strains and for B/Yamagata but not for the B/Victoria lineage strain (UB of the 95% CI for the GMT ratio of 1.71).

Reviewer comment: Post-vaccination HI GMTs against B/Victoria were statistically significantly lower for Flublok RIV4 as compared to IIV4 with non-overlapping 95% CIs. However, immune responses to B/Victoria were low in both treatment groups and, most likely, may be related to a study population relatively immunologically naïve to influenza B viruses, especially to B/Victoria, as evidenced by the low baseline GMTs relative to those against the influenza A/H3 and A/H1 antigens. Lower responses to B strains as compared to type A strains have been observed in other clinical trials of inactivated influenza vaccines. Whether other factors contributed to the very low responses to B/Victoria, particularly in the Flublok RIV4 group, is unclear. Such factors might include the use of whole virus and not split virus or rHA antigen in the HI assay (see Section 4.2), use of egg-derived antigen in the HI assay, loss of glycosylation site(s) during egg adaptation for B/Brisbane, interference from other vaccine antigens, or suboptimal potency. This issue was discussed with the DVP reviewer who felt that interference from the other non-replicating vaccine components was biologically unlikely and excluded suboptimal potency as contributory. Please see the related discussion below and the DVP review for additional information.

Table 15 presents the results of Day 28 post-vaccination SCRs and SCR differences between Flublok RIV4 and IIV4 for each vaccine antigen (Immunogenicity Population).

Table 15: Day 28 Post-Vaccination HI SCRs and SCR differences between Flublok Quadrivalent and IIV4 in Adults 18 through 49 Years of Age – PSC16 (Immunogenicity Population)

Strain	RIV4 SCR N=969 % (95% CI)	IIV4 SCR N=323 % (95% CI)	SCR Difference % (95% CI)	Met SCR Criteria?*
A/H1N1	66.7 (63.6,69.6)	63.5 (58.0,68.7)	-3.2 (-9.2,2.8)	Yes
A/H3N2	72.1 (69.2,74.9)	57.0 (51.4,62.4)	-15.2 (-21.3,-9.1)	Yes
B /Yamagata	59.6 (56.5,62.8)	60.4 (54.8,65.7)	0.7 (-5.4,6.9)	Yes

Strain	RIV4 SCR N=969 % (95% CI)	IIV4 SCR N=323 % (95% CI)	SCR Difference % (95% CI)	Met SCR Criteria?*
B/Victoria	40.6 (37.4,43.7)	58.2 (52.6,63.6)	17.6 (11.4,23.9)	No

Source: STN 125285/194.9, Module 5, PSC16 CSR, Tables 14.2.1.2 (07Mar2016).
Abbreviations: HI=hemagglutinin inhibition; RIV4=Flublok Quadrivalent; IIV4=Fluarix Quadrivalent; SCR=seroconversion rate.
*Success criteria for the SCR difference (SCR_{IIV4} - SCR_{RIV4}): UB of the 95% CI must be ≤ 10%.

Flublok RIV4 met pre-specified success criteria for non-inferior SCRs as compared to IIV4 for both influenza type A strains and B/Yamagata but not for the B/Victoria strain (UB of the 95% CI for the SCR difference of 23.9%).

Reviewer comment: Although lower immune responses to influenza B viruses relative to type A viruses are not unusual, Flublok recipients had significantly lower SCRs to the B/Victoria strain as compared to IIV4. The Applicant stated that the lower responses to the B strain virus may be related to mutations in B hemagglutinin that occur during adaptation to growth in eggs and to observations that antibodies raised in ferrets to B/Brisbane/60/2008 vaccine manufactured in cell culture (MDCK) react poorly with egg-based B/Brisbane/60/2008 antigen and yield lower HI titers in an egg-based HI assay as compared to antibodies raised by egg-based vaccine. Additionally, during the annual influenza strain selection meeting on February 23, 2016, the VRBPAC indicated that egg-grown B/Brisbane/60/2008 often loses a glycosylation site resulting in a difference between egg-grown and cell-grown antigenic structure and potential differences in HI titers if the "matched" antigen is not used in the HI assay. Per discussion with DVP, antigenic differences between egg-based and rHA-derived B/Brisbane antigens could similarly result in lower HI titers for rHA B/Brisbane when egg-derived antigen is used in the HI assay. Thus, the reasons for the lower immune response to the B/Victoria lineage vaccine antigen in Flublok RIV4 recipients and how this might influence clinical efficacy are not completely clear, but may relate in part to the use of egg-derived antigen (in the form of whole virus) in the HI assay. Although rHA HI titers to B strains may be lower if egg-derived rather than rHA antigen is used in the assay, we would not expect this alone to impact clinical efficacy because the recombinant HA vaccine sequence for the B strain should remain close to the reference wildtype virus strain. Because HI titers for the B strain are difficult to interpret, evaluation of vaccine efficacy rather than immunogenicity may be preferable in future studies of Flublok RIV4, e.g., in the pediatric population.

In the study report for PSC16, the Applicant stated that the protective efficacy of Flublok RIV4 against the two B strains in older adults (PSC12) was similar to IIV4 based on Kaplan-Meier curves (time to rt-PCR-confirmed febrile ILI), and that this supported the efficacy of Flublok RIV4 against B/Brisbane/60/2008 despite the lower immunogenicity results observed in PSC16. However, post hoc analyses conducted in PSC12 for rt-PCR-confirmed influenza B indicated a relative VE of 4% with a LB of the 95% CI lower than the NI criterion of -20%, [95% CI: -72%, 46%]. Additionally, the rVE for influenza B was based on cases from both B virus lineages (Flublok RIV4 n=23, IIV4 n=24). The sponsor did not distinguish between lineages in their report but CDC surveillance found that approximately 85% of

circulating influenza B viruses in 2014-2015 were B/Massachusetts (Yamagata lineage) which were well-matched to the vaccine antigens. Although the sub-analyses show a trend toward similar rVE of Flublok RIV4 against the B strains as compared to IIV4, these data primarily reflect the predominant B/Yamagata strain and remain inconclusive because the LB of the 95% CI includes zero. In the reviewer's opinion, the rVE data from PSC12 for the B strain do not completely reassure or provide support for the Applicant's explanation for the very low immunogenicity of Flublok RIV4 against B/Brisbane/60/2008. Please see the DVP and Statistical reviews for additional discussion. [16,79]

Reviewer comment: In the PSC16 CSR (Section 11.1 and 11.4.2.6), the Applicant stated that they conducted immunogenicity analyses on the Per Protocol (PPP) population as a sensitivity analysis to assure that the Immunogenicity Population yielded results consistent with those from subjects who were fully compliant with the protocol. However, the sponsor did not provide or comment on the results of the PPP analysis in the CSR. In response to an IR regarding this issue, (STN 125285/194.2), the Applicant clarified that the SAP did not define a PPP and that a sensitivity analysis was not actually performed as they had stated in the CSR. In response to our follow-up IR (STN 125285/194.4), the Applicant conducted a post hoc sensitivity analysis of the primary immunogenicity endpoint based on the protocol-defined PPP (data not shown). The results of this analysis were very similar to those of the primary endpoint analysis using the Immunogenicity Population. Sub-analyses according to sex, race and ethnicity were also very similar to analyses based on the IP.

6.1.11.2 Analyses of Secondary Endpoints

Secondary immunogenicity endpoints were SCRs and the proportion of subjects in each treatment group with post-vaccination HI titers ≥1:40 (% HI ≥1:40). The LBs on the 95% CI for SCRs to each vaccine antigen according to treatment group were presented in Table 15, Section 6.1.11.1, and show that both Flublok RIV4 and IIV4 recipients met immune response success criteria (the LB of the 2-sided 95% CI for the SCR must be ≥ 40%) for A/H1N1, A/H3N2, and B/Yamagata. Flublok RIV4 did not meet the SCR success criteria for B/Victoria in contrast to IIV4 (LBs of the 95% CI of 37.4% and 52.6%, respectively).

Table 16 presents results for the % HI ≥1:40 according to treatment group:

Table 16: Proportion of Subjects with Day 28 Post-Vaccination HI titer ≥1:40 – PSC16 (Immunogenicity Population)

Strain	Flublok RIV4 N=969 % (95% CI)	Met Success Criteria?*	IIV4 N=323 % (95% CI)	Met Success Criteria?*
A/H1N1	98.2 (97.2,99.0)	Yes	99.1 (97.3,99.8)	Yes
A/N3N2	99.7 (99.1,99.9)	Yes	97.1 (97.3,99.8)	Yes
B/Yamagata	91.0 (89.0,92.7)	Yes	92.0 (88.4,94.7)	Yes
B/Victoria	64.3 (61.2,67.3)	No	79.6 (74.8,83.8)	Yes

Source: STN 125285/194, Module 5, PSC16 CSR, Table 14.2.2.1
Abbreviations: HI=hemagglutinin inhibition; RIV4=Flublok Quadrivalent; IIV4=Fluarix QIV
*Success criteria: The LB of the 2-sided 95% CI for the % ≥ 1:40 must be ≥ 70%.

Reviewer comment: Consistent with results of SCR and GMT endpoints, the post-vaccination % HI ≥1:40 demonstrated lower immune responses for B/Victoria in

both treatment groups. However, only Flublok RIV4 failed to meet success criteria for this strain and parameter, i.e., that the LB of the 95% CI must be ≥70% (Flublok 61.2%, IIV4 74.8%).

6.1.11.3 Subpopulation Analyses

Sex

Subanalyses according to sex demonstrated similar post-vaccination GMTs and SCRs both between males and females, and as compared to the overall IP, for each vaccine antigen. Similar to the overall population, the UBs of the 95% CI for post-vaccination GMT ratios met success criteria for the non-inferiority of Flublok as compared to IIV4 in both males and females for the A/H1N1, A/H3N2, and B/Yamagata strains but not for B/Victoria. Males and females met criteria for non-inferior SCR differences for the A/H1N1 and A/H3N2 antigens. Females but not males met criteria for a non-inferior SCR difference for B/Yamagata. Neither males nor females met success criteria for a non-inferior SCR difference for the B/Victoria antigen.

Race

Subanalyses according to race demonstrated similar post-vaccination GMTs and SCRs with overlapping 95% CIs between whites/Caucasians and blacks/African Americans for each vaccine antigen in both treatment groups. GMT ratios in these two groups were similar and met success criteria for the non-inferiority of Flublok RIV4 as compared to IIV4 for the A/H1N1, H3N2, and B/Yamagata strains but not for B/Victoria. Both blacks and whites met success criteria for non-inferior SCR differences for A/H1N1 and A/H3N2 but not for B/Yamagata or B/Victoria. Numbers of subjects were too small and confidence intervals too wide to draw meaningful conclusions from immunogenicity subanalyses of racial groups other than blacks or whites.

Ethnicity

Post-vaccination GMTs and SCRs in Hispanics and non-Hispanics were not significantly different, and within these subgroups, GMTs and SCRs were also similar between treatment groups. The UBs of the 95% CI for GMT ratios were similar between Hispanics and non-Hispanics, and both groups met success criteria for the non-inferiority of Flublok RIV4 for the A/H1N1, A/H3N2, and B/Yamagata antigens but not for B/Victoria. The UBs of the 95% CI for SCR differences were similar, and both subgroups met success criteria non-inferiority for the A/H1N1 antigen. For A/H3N2 and B/Yamagata, non-Hispanics met success criteria for non-inferiority but Hispanics failed to meet these criteria. Neither subgroup met success criteria for a non-inferior SCR difference for the B/Victoria antigen.

Reviewer comment: No consistent or clearly disparate trends in post-vaccination GMTs, SCRs or non-inferiority analyses were observed among sex, racial, or ethnic subpopulations as compared to the overall population. The numbers of subjects representing racial groups other than blacks or whites were too small to draw meaningful conclusions from immunogenicity subanalyses.

6.1.11.4 Dropouts and/or Discontinuations

The Immunogenicity Population comprised 95.7% of the total randomized and vaccinated study population. Dropouts were not replaced and missing data was not imputed. Because the percentage of subjects excluded from the IP was low and

balanced between treatment groups, discontinuations should not have created a bias in the immunogenicity results.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

6.1.12.1 Methods

The Reactogenicity Population (RP) included all subjects who received known study vaccine and provided data on at least one day of the 7-day Memory Aid A for a given category of reactogenicity event. The RP was sub-divided into three categories for injection site, systemic, and febrile reactions, and was used for the analyses of pre-specified solicited AEs as described in Section 6.1.10.1. Solicited AEs were actively collected via a memory aid for seven days post-vaccination.

The Safety Population (SP) included all subjects who received a dose of study vaccine and for whom any safety data were available after vaccination, and was used for the analyses of unsolicited AEs, SAEs, and MAEs. Spontaneous, unsolicited, treatment-emergent AEs were passively collected for twenty-eight days post-vaccination and recorded on Memory Aid B. SAEs and MAEs were passively collected for six months post-vaccination. Please see Section 6.1.7 for details of safety monitoring.

6.1.12.2 Overview of Adverse Events

Of the total 1350 subjects who were randomized and vaccinated with a single dose of study vaccine, 1330 provided at least some safety data following vaccination and were included in the Safety Population. A total of 1328 and 1326 subjects, respectively, provided solicited local and systemic AE data for the Reactogenicity Populations A and B, respectively, and 1317 subjects provided solicited body temperature data for Reactogenicity Population C.

Tables 17 and 18 present an overview of solicited and unsolicited treatment-emergent adverse events (TEAEs), respectively, according to study vaccine.

Table 17: Overview of Solicited Adverse Events Occurring Day 0 through Day 7 Post-Vaccination–PSC16 (Reactogenicity Population)

Category	**Flublok Quadrivalent N=996 n(%)**	**IIV4 N=332 n(%)**
Any solicited AE	609 (61.1)	205 (61.7)
• Grade 3	32 (3.2)	13 (3.9)
• Grade 4	1 (0.1)	1 (0.3)
Any solicited injection site reaction[1]	509 (51.1)	172 (51.8)
• Grade 3	11 (1.1)	5 (1.5)
• Grade 4	0	0
Any solicited systemic AE[2]	339 (34.1)	119 (35.8)
• Grade 3	23 (2.3)	9 (2.7)
• Grade 4	1 (0.1)	1 (0.3)
Any solicited febrile reaction[3]	15 (1.5)	2 (0.6)
• Grade 3	4 (0.4)	1 (0.3)
• Grade 4	0	0

Source: STN 125285/194.2, Module 5, PSC16 CSR, Table 14.3.2.7.1 and evaluation of the electronic datasets.
[1]Denominators for solicited injection site reactions (Reactogenicity Population A): Flublok n=996; IIV4 n=332.
[2]Denominators for solicited systemic AEs (Reactogenicity Population B): Flublok n=994; IIV4 n=332.
[3]Denominators for febrile reactions (Reactogenicity Population C): Flublok n=990; IIV4 n=327.

Table 18: Overview of Unsolicited Treatment-Emergent Adverse Events Occurring from Day 0 through Day 180 Post-Vaccination– PSC16 (Safety Population)

Category	**Flublok Quadrivalent N=998 n(%)**	**IIV4 N=332 n(%)**
Any unsolicited TEAE	143 (14.3)	47 (14.2)
-Grade 1 (mild)	72 (7.2)	24 (7.2)
-Grade 2 (moderate)	54 (5.4)	19 (5.7)
-Grade 3 (severe)	17 (1.7)	4 (1.2)
-Grade 4 (life-threatening)	0	0
• Treatment-related TEAEs*	18 (1.8)	6 (1.8)
TEAEs leading to discontinuation	0	0
Serious TEAEs (SAEs)	10 (1.0)	2 (0.6)
• Treatment-related serious TEAEs (SAEs)*	0	0
Deaths	0	0
Any MAE	81 (8.1)	24 (7.2)
• Treatment-related MAEs*	2 (0.2)	2 (0.6)

Source: STN 125285/194, Module 5, PSC16 CSR, Tables 14.3.2.1 and 14.3.2.3.1 and evaluation of the electronic datasets.
*Relatedness as assessed by the investigator.

Reviewer comment: The incidence of solicited AEs was similar between treatment groups. IIV4 recipients reported slightly higher rates of severe (Grade 3) solicited local (1.5% vs 1.1%, respectively) and systemic (2.7% vs 2.3%, respectively) as compared to Flublok RIV4 recipients. More Flublok RIV4 recipients reported post-vaccination fever as compared to IIV4 (1.5% vs 0.6%, respectively), however, the rates of severe (Grade 3) fever were similar between treatment groups (0.4% vs 0.3%, respectively).

Reviewer comment: The overall incidence of unsolicited TEAEs was similar between treatment groups. Flublok RIV4 recipients reported slightly higher rates of severe (Grade 3) TEAEs (1.7% vs 1.2%, respectively), SAEs (1.0% vs 0.6%, respectively), and MAEs (8.1% vs 7.2%, respectively) as compared to IIV4 recipients. However, no clinically significant imbalances in specific types of events were identified. Proportions of events assessed as related between treatment groups were either the same (TEAEs 1.8%) or lower in Flublok RIV4 recipients as compared to IIV4 (MAEs 0.6% vs 0.2%, respectively). Evaluation of the electronic datasets was consistent with the sponsor's report.

Solicited Adverse Events

Solicited Local AEs

Table 19 summarizes the rates of solicited local AEs reported in the seven days following vaccination (Day 0 through Day 7) in subjects 18-49 years of age according to treatment group, overall and by maximum severity grade.

Table 19: Solicited Local Injection Site Reactions, Day 0 through Day 7 Post-Vaccination, Subjects Aged 18-49 Years – PSC16 (Reactogenicity Population)

Treatment	RIV4 N=996	RIV4 N=996	RIV4 N=996	IIV4 N=332	IIV4 N=332	IIV4 N=332
Severity Grade	**Any**	**Grade 3**	**Grade 4**	**Any**	**Grade 3**	**Grade 4**
Local Solicited AE	**n(%)[1]**	**n(%)[2]**	**n(%)[2]**	**n(%)[1]**	**n(%)[2]**	**n(%)[2]**
Any Local AE[1]	509 (51.1)	11 (1.1)	0*	172 (51.8)	5 (1.5)	0
Local pain[2]	367 (36.8)	9 (0.9)	0	121 (36.4)	3 (0.9)	0
Local tenderness[2]	477 (47.9)	9 (0.9)	0*	155 (46.7)	4 (1.2)	0
Local redness[2]	42 (4.2)	0	0	3 (0.9)	0	0
Local firmness/swelling[2]	49 (4.9)	0	0	10 (3.0)	0	0

Source: STN 125285/194.2, Module 5, PSC16 CSR, Table 14.7.2.3.7.1 and evaluation of the electronic datasets.
RIV4=Flublok Quadrivalent, IIV4=Fluarix Quadrivalent.
[1]n represents the number of subjects in each treatment group who experienced symptoms even if severity grades were missing; denominator for percentage is number of subjects in the Reactogenicity Population A for the treatment group: RIV4 n=996; IIV4 n=332.
[2]Denominator for the percentage excludes subjects in each treatment group who were missing severity data for all 7 days of the solicited AE period: for RIV4, n=996; for IIV4 n=332 (for all parameters).
*A data entry error was made for Flublok recipient 54-61303 whose Memory Aid A showed all Grade 0 events for reactogenicity instead of Grade 4 as reported in the CRF and CSR. The sponsor corrected the error in a response to CBER's IR (STN 125285/194.2).

The most common local reactogenicity events following study vaccinations were injection site tenderness (Flublok 47.9%, IIV4 46.7%) and pain (Flublok 36.8%, IIV4 36.4%), mostly Grade 1 to Grade 2 (mild to moderate) in severity. Rates and severity of local injection site reactions were similar between treatment groups except for redness which occurred more frequently among Flublok as compared to IIV4 recipients (4.2% vs 0.9%, respectively). Grade 3 reactions were uncommon (0.0%-1.2%). No Grade 4, life-threatening, solicited injection site reactions were reported. Local reactions began between Days 0 and 1 in the majority of subjects and had a mean duration of 2.0-2.3 days, similar between treatment groups.

Solicited Systemic AEs including Fever

Table 20 summarizes the rates of solicited systemic AEs reported in the seven days following vaccination (Day 0 through Day 7) in subjects 18-49 years of age according to treatment group, overall and by maximum severity grade.

Table 20: Solicited Systemic Adverse Events and Fever, Day 0 through Day 7 Post-Vaccination, Subjects Aged 18 through 49 Years – PSC16 (Reactogenicity Population)

Treatment	RIV4 N=996	RIV4 N=996	RIV4 N=996	IIV4 N=332	IIV4 N=332	IIV4 N=332
Severity Grade	**Any**	**Grade 3**	**Grade 4**	**Any**	**Grade 3**	**Grade 4**
Systemic Solicited AE	**n(%)[1]**	**n(%)[2]**	**n(%)[2]**	**n(%)[1]**	**n(%)[2]**	**n(%)[2]**
Any Systemic AE[1]	339 (34.1)	23 (2.3)	1 (0.1)	119 (35.8)	9 (2.7)	1 (0.3)
Fatigue[2]	164 (16.5)	5 (0.5)	0	55 (16.6)	4 (1.2)	0
Shivering/chills[2]	69 (6.9)	5 (0.5)	0	20 (6.0)	4 (1.2)	0
Joint pain[2]	94 (9.5)	9 (0.9)	0	34 (10.2)	2 (0.6)	0
Muscle pain[2]	127 (12.8)	9 (0.9)	0	39 (11.7)	3 (0.9)	0
Headache[2]	202 (20.3)	13 (1.3)	0	70 (21.1)	6 (1.8)	1 (0.3)
Nausea[2]	89 (9.0)	6 (0.6)	1 (0.1)	31 (9.3)	4 (1.2)	0
Fever[3]	15 (1.5)	4 (0.4)	0	2 (0.6)	1 (0.3)	0

Source: Adapted from STN 125285/194, Module 5, PSC16 CSR, Table 14.3.2.7.1 and evaluation of the electronic datasets.
RIV4=Flublok Quadrivalent, IIV4=Fluarix Quadrivalent.
[1]n represents the number of subjects in each treatment group who experienced symptoms even if severity grades were missing; denominator for percentage is number of subjects in the Reactogenicity Population B for the treatment group: RIV4 n=994; IIV4 n=332.
[2]Denominator for the percentage excludes subjects in each treatment group who were missing severity data for all 7 days of the solicited AE period: for RIV4, n=994; for IIV4 n=332 (for all parameters).
[3]Denominator for the percentage excludes subjects in each treatment group who were missing severity data for all 7 days of the solicited AE period for fever: RIV4 n=990; IIV4 n=327. Grade 1=100.4°F-101.1°F; Grade 2=101.2°F-102.0°F; Grade 3=102.1°F-104°F; Grade 4>104°F.

Approximately 35% of the study population experienced at least one solicited systemic AE. Individual events occurred at similar rates between treatment groups except for fever which was uncommon but occurred almost three times more frequently in Flublok RIV4 recipients as compared to IIV4 (1.5% vs 0.6%, respectively). The rate of severe (Grade 3) fever was similar between treatment groups (Flublok 0.4%, IIV4 0.3%), and no subjects had fever >104°F. The most commonly reported symptoms were headache (Flublok 20.3%, IIV4 21.1%) fatigue (Flublok 16.5%, IIV4 16.6%), muscle pain (Flublok 12.8, IIV4 11.7%), and joint pain (Flublok 9.5%, IIV4 10.2%). Most symptoms were mild to moderate (Grade 1 or Grade 2) in severity. Similar proportions of Flublok and IIV4 recipients (2.3% vs 2.7%, respectively) reported having any Grade 3 solicited systemic symptom (excluding fever). Grade 4 events were rare: one Flublok recipient had Grade 4 nausea and one IIV4 recipient had Grade 4 headache, both of which resolved by Day 7. Most solicited systemic symptoms began between Day 0 and Day 2, and persisted for a mean duration of 1.8 to 1.9 days in both treatment groups.

Sensitivity analyses performed by imputing a Grade 3 for missing data did not change the overall interpretation of the either solicited local or systemic AE results (data not shown, see PSC16 CSR Table 14.3.2.7.5).

Reviewer comment: Rates, severity, and duration of local and systemic reactogenicity events were consistent with previous clinical trial data for the trivalent formulation of Flublok and were similar between treatment groups. Evaluation of the electronic datasets was consistent with the sponsor's report.

Subpopulation analyses of Solicited Adverse Events

In both treatment groups, local injection site reactions were reported more frequently among females and whites as compared to males and non-whites [rates of any solicited local reaction 56.7% and 59.7% versus 41.2% and 40.1%, respectively. These differences were driven by local pain and tenderness. Rates of local pain and tenderness, respectively, in female as compared to male Flublok RIV4 recipients were 40.5% and 53.4% vs 30.4% and 38.4%. Rates of local pain and tenderness, respectively, in white as compared to non-white Flublok RIV4 recipients were 43.2% and 56.0% vs 27.7% and 36.5%. Females reported slightly more systemic symptoms overall as compared to males (38.2% versus 26.8%), the largest difference being in the frequency of headache (23.0% vs 15.6%). There were only small differences in the rates of solicited systemic symptoms between whites and non-whites (rates of any systemic symptom 36.3% vs 30.9%, respectively). Overall, non-Hispanics/Latinos had higher rates of any solicited AE than Hispanics/Latinos (62.8% vs 53.4%, respectively), with local tenderness accounting for much of the difference (49.3% vs 38.8%), and smaller differences observed between subgroups in the rates of other parameters.

Reviewer comment: A trend towards higher rates of solicited local and systemic AEs in females as compared to males has been observed in other clinical influenza vaccine studies. The numbers of subjects belonging to racial groups other than whites or blacks or of Hispanic ethnicity were too small for meaningful comparisons of the rates of solicited adverse events in these subpopulations.

Unsolicited treatment-emergent AEs (TEAEs) were collected immediately after vaccination through Day 28 and categorized according to MedDRA preferred term (PT) and system organ class (SOC). TEAEs included spontaneous reports, responses to general questions about current or interim health status, and any reactogenicity events that persisted beyond or began after the 7-day post-vaccination period covered by Memory Aid A (Days 0-7). Subjects were counted once per PT and per SOC, once per maximum intensity for each category, and once by closest relationship to study vaccine. Based on the judgment of the investigators, some laboratory abnormalities obtained in the evaluation of AEs were reported as unsolicited AEs.

A total of 138 (10.4%) subjects reported TEAEs in the 28 days following vaccination, with similar proportions between treatment groups: Flublok RIV4 10.3% vs IIV4 10.5%. System Organ Class categories with the highest overall rates of AEs in the Flublok and IIV4 treatment groups, respectively, were: Infections and Infestations (3.0% vs 3.3%), primarily nasopharyngitis (0.4% vs 1.2%); Respiratory, Thoracic, and Mediastinal Disorders (2.2% vs 1.5%), primarily cough (1.1% vs 0.9%); Nervous System Disorders (2.0% vs 1.5%), primarily headache (1.8% vs 1.2%); Musculoskeletal and Connective Tissue Disorders (1.1% vs 2.7%), no single predominant event; Gastrointestinal Disorders (1.3% vs 1.5%), no single predominant event; and General Disorders and Administration Site Conditions (1.3% vs 0.9%), no single predominant event.

Most unsolicited AEs were mild to moderate in severity (5.8% and 3.5%, respectively, of the Safety Population through Day 28). A total of 11 (1.1%) and 3 (0.9%) of Flublok RIV4 and IIV4 recipients, respectively, reported severe (Grade 3) events. No subjects experienced life threatening (Grade 4) unsolicited AEs. A total of 1.7% of subjects in either group had TEAEs assessed as related to study vaccine. No TEAEs lead to discontinuation from the study.

Table 21 summarizes unsolicited TEAEs that occurred in either treatment group with a frequency of ≥1% post-vaccination from Day 0 through Day 28, whether by PT or SOC categories.

Table 21: Unsolicited Treatment-Emergent Adverse Events Reported by ≥1% of Subjects 18-49 Years of Age from Day 0 through Day 28 by Treatment Group* – PSC16 (Safety Population)

System Organ Class/ Preferred Term	Flublok RIV4 N=998 n(%)	IIV4 N=332 n(%)
One or more AEs	103 (10.3)	35 (10.5)
-Grade 1 (mild)	56 (5.6)	21 (6.3)
-Grade 2 (moderate)	36 (3.6)	11 (3.3)
-Grade 3 (severe)	11 (1.1)	3 (0.9)
-Grade 4 (life-threatening)	0	0
One or more related AEs	18 (1.8)	5 (1.5)
Infections and Infestations	30 (3.0)	11 (3.3)
-nasopharyngitis	4 (0.4)	4 (1.2)
Respiratory, thoracic, and mediastinal disorders	22 (2.2)	5 (1.5)
-cough	11 (1.1)	3 (0.9)

System Organ Class/ Preferred Term	Flublok RIV4 N=998 n(%)	IIV4 N=332 n(%)
Nervous System Disorders	20 (2.0)	5 (1.5)
-headache	18 (1.8)	4 (1.2)
Gastrointestinal disorders	13 (1.3)	5 (1.5)
General disorders and administration site conditions	13 (1.3)	3 (0.9)
Musculoskeletal and connective tissue disorders	11 (1.1)	9 (2.7)

Source: STN 125285/194.2, Module 5, PSC16 CSR, Tables 22, 14.3.2.1.a, 14.3.2.2.1.a, 14.3.2.3.1.a, and evaluation of the electronic datasets.
*Any MedDRA System Organ Class (SOC) category or preferred term (PT) with an incidence of ≥1% in either treatment group is included in the table.
Bold type indicates system organ class.

Reviewer comment: The CSR summarized TEAEs from Day 0 through Day 180 instead of Day 0 through Day 28, as pre-specified, impacting the entire CSR. The Applicant submitted revised tables at CBER's request (STN 125285/194.2).

Severe Non-Serious Unsolicited AEs

Similar proportions of Flublok RIV4 and IIV4 recipients, 11 (1.1%) versus 3 (0.9%) respectively, reported severe (Grade 3) events (serious and non-serious through Day 28). No large imbalances were identified between treatment groups in the type of severe events reported as categorized by MedDRA SOC and PT. Severe non-serious unsolicited AEs were evaluated further in the electronic datasets. None of the events appeared related to study vaccines due to a lack of temporal relationship to vaccination, biological plausibility, and/or the sponsor's assessment of relatedness.

Subpopulation Analyses of Unsolicited Adverse Events

Overall, more females than males reported unsolicited AEs (Flublok RIV4 female vs male recipients 11.0% vs 9.2%; IIV4 female vs male recipients 12.2% vs 7.3%). The largest disparity was observed in the SOC category of Infections and Infestations (Flublok RIV4 female vs male recipients 3.3% vs 2.5%; IIV4 female vs male recipients 4.5% vs 0.9%). Rates and severity grades were generally similar between treatment groups overall and by SOC category (see STN 125285/194.2, PSC16 CSR Tables 14.3.2.2.2.a and 14.3.2.3.2a). More whites/Caucasians than non-whites reported unsolicited AEs for most SOC categories (overall, Flublok RIV4 white/Caucasian vs non-white recipients 13.1% vs 6.4%; IIV4 white/Caucasian vs non-white recipients 13.4% vs 6.2%). The largest disparity was observed in the SOC category of Infections and Infestations (Flublok RIV4 white/Caucasian vs non-white recipients 4.4% vs 1.0%; IIV4 white/Caucasian vs non-white recipients 5.0% vs 0.8%). Rates and severity grades were similar between treatment groups (see PSC16 CSR Tables 14.3.2.2.3.a and 14.3.2.3.3.a). Blacks/African Americans comprised the majority of non-white racial groups. Ethnicity did not appear to influence the incidence or severity of unsolicited AEs (overall incidence for Flublok RIV4 Hispanic/Latino vs non-Hispanic/Latino recipients 8.0% vs 10.8%; IIV4 Hispanic/Latino vs non-Hispanic/Latino recipients 8.8% vs 10.9%). See PSC16 CSR Tables 14.3.2.2.4.a and 14.3.2.3.4.a for additional information.

6.1.12.3 Deaths

No deaths occurred during the six month post-vaccination follow-up period.

6.1.12.4 Nonfatal Serious Adverse Events

A total of ten (1.0%) Flublok RIV4 and 2 (0.6%) of IIV4 recipients experienced SAEs during the six month post-vaccination follow-up period. Of these, three (0.6%) Flublok RIV4 recipients had three SAEs and no IIV4 recipients had SAEs during the 28 days post-vaccination. None of the SAEs (Day 0-180) were assessed as related to study vaccines by the Applicant or investigators.

Table 22 summarizes SAEs that occurred from Days 0 through 180 post-vaccination according to treatment group and MedDRA SOC and PT. SAEs that occurred from Days 0 through 28 are marked with an asterix.

Table 22: Serious Adverse Events Days 0 through 180 – PSC16 (Safety Population)

System Organ Class Preferred Term	**Flublok N=998 n(%)**	**IIV4 N=332 n(%)**
Any SAE	10 (1.0)	2 (0.6)
Gastrointestinal disorders	1 (0.1)	2 (0.6)
-gastrointestinal hemorrhage	0	1 (0.3)
-pancreatitis	0	1 (0.3)
-small intestinal obstruction	1 (0.1)	0
Cardiac disorders	2 (0.2)	0
-myocardial infarction	2 (0.2)	0
Infections and infestations	2 (0.2)	0
-appendicitis*	1 (0.1)	0
-periumbilical abscess*	1 (0.1)	0
Hepatobiliary disorders	0	1 (0.3)
-cholecystitis	0	1 (0.3)
Injury, poisoning, and procedural complications	1 (0.1)	0
-road traffic accident	1 (0.1)	0
Musculoskeletal and connective tissue disorders	1 (0.1)	0
-neck pain	1 (0.1)	0
Nervous system disorders	1 (0.1)	0
-metabolic encephalopathy	1 (0.1)	0
Pregnancy, puerperium and perinatal conditions	1 (0.1)	0
-abortion spontaneous	1 (0.1)	0
Reproductive system and breast disorders	1 (0.1)	0
-ovarian cyst	1 (0.1)	0
Surgical and medical procedures	1 (0.1)	0
-arm amputation*	1 (0.1)	0

Source: STN 125285/194, Module 5, PSC16 CSR Tables 14.3.2.6.1 and 14.3.2.6.2 and evaluation of the electronic datasets.
*Signifies onset from post-vaccination Day 0 through Day 28.

Reviewer comment: Although relatively more Flublok RIV4 than IIV4 recipients had SAEs during the six month follow-up period, individual types of events occurred in very low numbers (0-1) with no large imbalances observed between treatment groups when categorized by body organ system. Subpopulation analyses of SAEs according to sex, race, and ethnicity [provided at CBER's request (STN 125285/194.3)] revealed no large imbalances or trends. One case narrative is provided below because it occurred in a female who became pregnant following vaccination with Flublok Quadrivalent:

Subject #(b) (6) was a 26 year old white, non-Hispanic/Latino female with a history of degenerative disk disease of the lower back and moderate spinal scoliosis who was vaccinated with Flublok RIV4 on (b) (6) . Urine pregnancy test prior to

vaccination was negative. She reported no fever or reactogenicity (all Grade 0) on her Memory Aid A and no concomitant medications. She returned to the study site on (b) (6) for Day 28 HI titers, and subsequently reported pregnancy on November 19, 2014 (per review of eCRF under "protocol deviations"). On (b) (6) (68 days post-vaccination) she presented to a clinic with a suspected miscarriage. She underwent dilation and curettage and was discharged home without apparent sequelae. The event was recorded in the CRF as an "abortion spontaneous", severe, serious, and assessed as not related to study vaccine by the investigator and Applicant. She was subsequently lost to follow up and did not complete the study or return Memory Aid B. In response to a January 11, 2016 request for additional information regarding this SAE, the Applicant responded that no other information was provided regarding evaluation of this event.

Reviewer comment: The rate of spontaneous abortion in early pregnancy (<20 weeks gestation) in females <35 years of age is approximately 15% and increases with age. Rates are higher in females with risk factors such as prior miscarriage and smoking, and are much higher in studies where clinically unrecognized pregnancy was diagnosed by measuring daily urine hCG levels. There is no known association between inactivated influenza vaccines and spontaneous abortion. Influenza vaccination is recommended in pregnant females. A pregnancy registry will be established for Flublok. [1,3,62]

Reviewer comment: The remaining SAE narratives and case report forms (CRFs) were reviewed and were notable for a lack of detailed information (see Section 3.1). Nevertheless, the reviewer agrees with the Applicant and investigators' assessments that none of the SAEs appeared related to study vaccines due to a lack of close temporal relationship, lack of biological plausibility, and/or the presence of a more likely pathophysiological mechanism.

6.1.12.5 Adverse Events of Special Interest (AESI)

Medically-Attended Events (MAEs)

Overall, a slightly higher proportion of Flublok RIV4 recipients experienced MAEs as compared to IIV4 recipients (8.0% vs 7.2%, respectively), with the only relatively large imbalances observed in Injury, Poisoning, and Procedural Complications (0.8% vs 0.3%, respectively) and Pregnancy, Puerperium and Perinatal Conditions (0.6% vs 0). Within these categories, the only notable imbalance identified for a specific event was the occurrence of seven (0.7%) Flublok recipients versus no IIV4 recipients who became pregnant during the study including one subject who had a spontaneous abortion (see Section 6.1.12.4). The rate of medically-attended "influenza-like illness" was the same in both treatment groups (0.3%). One additional Flublok RIV4 recipient had "influenza" diagnosed on Study Day 16. Subpopulation analyses of MAEs (STN 125285/194.3) revealed that higher proportions of females, whites/Caucasians, and non-Hispanic/Latinos had MAEs as compared to males, non-whites/Caucasians, or Hispanic/Latinos. Because overall rates were low, the significance of these trends is uncertain.

Reviewer comment: It is possible that the case of influenza in a Flublok recipient diagnosed on Day 16 may have occurred prior to a protective immune response from vaccination. The explanation for the very small imbalance of pregnancies in this small study is not apparent. Review of MAEs was otherwise unremarkable.

AESIs

The study protocol did not define AESIs as specific safety endpoints. However, the CSR and electronic datasets were evaluated for events representing potential risks that have been associated with influenza vaccines and that PSC monitors as part of its pharmacovigilance plan: hypersensitivity, including anaphylaxis and serum sickness, encephalomyelitis, transverse myelitis, Guillain-Barre syndrome (GBS), Bell's Palsy, optic neuritis, and seizures or convulsions. Due to one case of unexplained pleuropericarditis reported in an earlier study (PSC04, please see the clinical review of the original BLA), the datasets were also evaluated for cases of pleuritis, pleuropericarditis, pericarditis, and myocarditis, but none were found. Apart from hypersensitivity type events (discussed separately below), one AESI was found:

- Subject (b) (6) was a 21 year old white male vaccinated with Flublok RIV4 on (b) (6) who had a seizure on February 16, 2015. The seizure was attributed to a past history of cardiovascular stroke and was treated with levetiracetam (Keppra). The event was assessed as moderate, non-serious, and not related to study vaccine.

Reviewer comment: The reviewer agrees with the sponsor's assessment of causality.

Hypersensitivity Type Events

Collection and analyses of acute hypersensitivity events were not pre-specified in this study. However, the reviewer evaluated the CSR and electronic datasets post hoc for potential acute hypersensitivity type events (searched adverse event terms including but not limited to: hypersensitivity, adverse drug reaction, allergy, anaphylaxis, hives, urticaria, bronchospasm, wheezing, rash, drug eruption, pruritis, edema, swelling, swelling face, swollen tongue, swollen lip, angioedema, asthma, allergic asthma, immune system disorder, serum sickness, vasculitis, and immune thrombocytopenia) . A total of 13 subjects (all Flublok RIV4 recipients) were identified as having potential hypersensitivity type events over the 180 day study period. Of the 13 subjects and 13 AEs, 12 events occurred within 5 days of vaccination and one (diarrhea) occurred on Day 19. Events that occurred within 7 days of vaccination (Day 0 through Day 7) are summarized in Table 23 according to MedDRA SOC and PT and treatment group. For diarrhea, which can be a manifestation of anaphylaxis, only cases that began within two days of vaccination are included summary Table 23.

Table 23: Summary of Potential Hypersensitivity Events Occurring from Day 0 through Day 7 Post-Vaccination according to Treatment Group – PSC16 (Safety Population)*

System Organ Class -Preferred term	**Flublok N=998 n(%)**	**IIV4 N=332 n(%)**
Gastrointestinal disorders		
-diarrhea	3 (0.3)	0
Respiratory, thoracic and mediastinal disorders		
-bronchospasm	1 (0.1)	0
Skin and subcutaneous tissue disorders		
-pruritis	5 (0.5)	0
-rash	1 (0.1)	0

Source: STN 125285/194, Module 5, PSC16 CSR, Tables 14.3.2.2.1 and 14.3.2.3.1 and evaluation of the electronic datasets.
*For diarrhea, only those cases with onset from Day 0 through Day 2 are included in the table.

Case narratives and CRFs were requested for eight cases based on potential relatedness to the study vaccines. Selected cases are summarized below.

- Subject (b) (6), a 30 year old Native Hawaiian/Pacific Islander female with a history of asthma, psoriasis and multiple medication allergies, on no maintenance therapy for asthma, was vaccinated with Flublok RIV4 on (b) (6). On (b) (6) (three days post-vaccination) she experienced bronchospasm and saw her physician who treated her with a five-day course of prednisone. The event was assessed as moderate, non-serious, not related to study vaccine, and resolved after six days.

Reviewer comment: This subject appeared to have a history of atopy or IgE-mediated allergic reactions. Given the onset of symptoms three days post-vaccination, the reviewer agrees that the cause of bronchospasm in this case was more likely an IgE-mediated response to an allergen other than study vaccine, however, study vaccine cannot be completely excluded as a precipitating event. Additionally, the investigator's assessment of this event as moderate in intensity could be questioned given the need for medical intervention and potential for interference with daily activity.

- Five Flublok RIV4 recipients had pruritus within 5 days of vaccination. All cases were mild and non-serious.
  - Subjects (b) (6) both had bilateral arm/palm itching without associated symptoms that began on Day 5 and were assessed as not related to study vaccine.
  - Subject (b) (6), a 47 year old black/African American female with no history of allergies, reported dry eyes, dry mouth and itching on Day 2, all of which were assessed as related to vaccination and resolved after 2 days.
  - Subject (b) (6), a 41 year old white female with a history of allergy to ibuprofen, developed itching, cough, and a metallic taste on the day of vaccination with Flublok RIV4, assessed as not related to study vaccine.
  - Subject (b) (6), a 36 year old white female with a history of seasonal allergies treated with cetirizine, developed pruritis involving the front of the neck without other symptoms on Day 1 following vaccination. Symptoms resolved spontaneously after one day and were assessed as related to study vaccine.
  - Subject (b) (6), a 29 year old black/African American male with a history of cervical spinal disc repair, developed a rash on his mouth, without associated symptoms, 5 days after receiving Flublok RIV4. The rash was not described further but was assessed as moderate, non-serious, and related to study vaccine. The rash resolved after 15 days without specific treatment.

Reviewer comment: AESIs and potential hypersensitivity type events possibly related to study vaccines were identified only in Flublok RIV4 recipients. However, the rates of such events were low (<0.5% for any specific event and <1% of Flublok recipients for all such events), and the imbalance between treatment groups was small and may have been due to chance alone. Additionally, most hypersensitivity-type events were mild, none were serious, and, for many, causality was uncertain. The Applicant indicated that they concurred with

investigators' assessments due to the lack of detailed descriptions or evaluations of the events, and was unable to provide additional information from source documents or the eCRFs. No definite severe or serious allergic reactions to either study vaccine were reported in this study, although the case of bronchospasm following receipt of Flublok Quadrivalent may have been related and may more appropriately been categorized as severe rather than moderate in intensity.

6.1.12.6 Clinical Test Results

Safety laboratories were not collected systematically in this study.

6.1.12.7 Dropouts and/or Discontinuations

Over 95% of subjects completed the study and provided safety follow-up data including 98.5% who provided any safety data and 92.5% who returned Memory Aid A at the Day 28 visit. Only six subjects discontinued before the Day 28 visit when vaccine-related AEs were more likely to occur. Most discontinuations were due to lost to follow-up (3.5%). No subjects were discontinued due to AEs.

6.1.13 Study Summary and Conclusions

Immunogenicity

Flublok RIV4 elicited immune responses, as measured by HI titers, that were non-inferior to IIV4, for the influenza A/H1N1, A/H3N2, and B/Yamagata strains contained in the vaccine.

Flublok RIV4 did not demonstrate non-inferior immunogenicity as compared to IIV4 for the B/Victoria strain. Additionally, Flublok did not meet success criteria for the secondary immune response endpoints of post-vaccination SCR and %HI ≥1:40 for B/Victoria whereas IIV4 did meet these criteria. Although lower immune responses to influenza B viruses as compared to type A have been observed in other clinical trials of inactivated influenza vaccines, the reasons for the very low responses and lower responses to the B/Victoria lineage virus relative to B/Yamagata in this study are not completely clear. Because responses to B/Brisbane/60/2008 were low at baseline and post-vaccination in both treatment groups, the most likely explanation may be that the study population was immunologically naïve to this strain. However, because higher responses to B/Brisbane/60/2008 were observed in a pilot study of children 6-17 years (PSC08), factors other than being immunologically naïve may be contributory. For example, use of whole virus (which yields lower titers) rather than split virus or rHA antigen in the HI assay, the possibility that antibodies elicited by an rHA-based vaccine are at a disadvantage when measured in an HI assay utilizing egg-derived antigen, or interference from the second B antigen. As mentioned in Section 6.1.11.1, interference from other non-replicating vaccine antigen components seemed biologically unlikely per discussion with the DVP reviewer, and, although we have no comparative data for Flublok RIV4 vs Flublok TIV-1 vs Flublok TIV-2 for evaluation, interference was not observed in studies of other QIVs. Suboptimal potency was not an issue contributing to low HI titers according to discussions with DVP. Given the uncertainty in interpreting these results, a clinical endpoint study conducted during a season when B/strains are more prevalent and antigenically well-matched to vaccines could be helpful in the assessment of the effectiveness of Flublok RIV4 against influenza B in adults. The review team discussed this option early in the review cycle and concluded that, because it is difficult to predict when ideal conditions may occur, it may not be feasible for the Applicant to conduct such an adult study at this time given the uncertainty of a

predominance of B/Victoria in any given season. However, we may learn more from planned pediatric assessments which the Applicant modified later in the review cycle to include an evaluation of efficacy.

In general, subanalyses of immunogenicity according to sex, black and white race, and Hispanic/Latino ethnicity reflected the overall study population and did not reveal consistent or distinct trends in post-vaccination GMTs or SCRs or non-inferiority analyses within subgroups or as compared to the overall population. The numbers of subjects representing racial groups other than blacks or whites were too small to draw meaningful conclusions from immunogenicity subanalyses.

Safety

Overall, the safety of Flublok RIV4 was acceptable and comparable to IIV4 in adults 18 through 49 years of age. Rates and severity of local injection site reactions, predominantly tenderness and pain, were similar between treatment groups except for local redness which occurred more frequently in the Flublok RIV4 group (4.2% vs 0.9%). Reactions were mostly mild to moderate (Grade 1 to Grade 2) in severity and short in duration. Solicited systemic adverse events, predominantly headache, fatigue, muscle pain, and joint pain, occurred at similar rates between treatment groups except for fever which was uncommon but occurred almost three times more frequently in Flublok RIV4 recipients as compared to IIV4 (1.5% vs 0.6%, respectively). Rates of severe (Grade 3) fever were similar between treatment groups (Flublok 0.4%, IIV4 0.3%). Most symptoms were mild to moderate (Grade 1 or Grade 2) in severity and short in duration.

The rates of TEAEs reported in the 28 days following vaccination were similar between treatment groups and were mostly mild to moderate in severity. No large imbalances, unusual patterns or safety concerns were identified. Subpopulation analyses revealed that more females than males and whites than non-whites reported unsolicited TEAEs. Ethnicity did not appear to influence the incidence or severity of unsolicited AEs.

No deaths or discontinuations due to AEs were reported in PSC16. A total of ten (1.0%) Flublok RIV4 and two (0.6%) IIV4 recipients experienced SAEs during the six month post-vaccination follow-up period. Of these, three (0.6%) Flublok RIV4 recipients had three SAEs while no IIV4 recipients had SAEs during the 28 days post-vaccination. Although more Flublok RIV4 than IIV4 recipients experienced SAEs, individual types of events occurred in very low numbers with no large imbalances between treatment groups observed when categorized by body organ system. None of the SAEs appeared related to study vaccines.

No subjects had noteworthy AESIs during the study other than possible hypersensitivity type events. Ten Flublok RIV4 but no IIV4 recipients were identified as having potential hypersensitivity type AEs such as bronchospasm, pruritus, or rash in the five days post-vaccination, or diarrhea within two days of vaccination. Most events were mild and non-serious, and, for many of the events, causality uncertain. Even if an allergic pathogenic mechanism and relationship to Flublok RIV4 were more certain, the overall imbalance of these events between treatment groups was small and may have been due to chance alone. No definite severe or serious allergic reactions were reported following either study vaccine although, in the reviewer's opinion, the case of bronchospasm three days after receiving Flublok RIV4 might more appropriately have been categorized as a severe event.

6.2 Trial #2 – PSC12

"Comparison of the Protective Efficacy of Flublok RIV4 versus Licensed Inactivated Influenza Vaccine (IIV4) in Healthy, Medically Stable Adults ≥50 Years of Age". NCT#: 02285998.

6.2.1 Objectives

Primary Objective

To compare the clinical efficacy of Flublok RIV4 to that of IIV4 with respect the ratio of attack rates of rt-PCR-confirmed protocol-defined influenza-like illness (ILI) that begin at least 14 days after vaccination caused by any influenza viral types/subtypes.

Secondary Objectives

- To compare the relative protective efficacy in prevention of respiratory illness and influenza infection beginning at least 14 days after vaccination among Flublok RIV4 recipients vs IIV4 recipients using several alternative case definitions.
- To compare the immunogenicity of Flublok RIV4 vs IIV4 in a pre-selected subset of subjects adequate to compare post-vaccination HI GMTs and SCRs for all four antigens in each study vaccine.
- To compare the safety and reactogenicity of Flublok RIV4 vs IIV4.

Exploratory Objectives

Efficacy and safety/reactogenicity will be assessed by subgroups defined by age category, sex, and race/ethnicity as exploratory analyses.

6.2.2 Design Overview

The study was a Phase 3, randomized, observer-blind, comparator-controlled, multicenter clinical trial designed to evaluate the relative vaccine efficacy (VE), immunogenicity, safety, and reactogenicity of Flublok RIV4 as compared to IIV4 in ~9000 ambulatory, medically stable adults 50 years of age and older. Subjects were randomized 1:1 to receive Flublok RIV4 or IIV4. Subjects and study staff, except for those who administered the study vaccines, were blinded to treatment. Relative vaccine efficacy (rVE) [1 – (Flublok RIV4 attack rate / IIV4 attack rate) x 100] for the primary analysis was based on rt-PCR-confirmed influenza (all strains regardless of antigenic similarity to vaccine antigens) associated with protocol-defined influenza-like illness (ILI). Non-inferior (NI) VE was pre-defined as a lower bound (LB) of the two-sided 95% CI for the rVE of Flublok RIV4 vs IIV4 of greater than -20%. If NI criteria were met, the protocol specified an exploratory criterion for superiority of a LB of the two-sided 95% CI for rVE of > +9%. The protocol provided for an extension of the study to a second season, if necessary, to accrue a sufficient number of cases for the primary analysis. The non-inferior immunogenicity of Flublok RIV4 as compared to IIV4 was assessed by evaluating HI titers on Days 0 and 28 collected from all subjects (n=614) enrolled at five pre-selected study sites (Sites 10, 14, 34, 37, and 39).

The safety of Flublok RIV4 and IIV4 was compared descriptively with respect to the incidence and severity of solicited and unsolicited adverse events. Subjects recorded solicited reactogenicity events during the 7 days following vaccine administration on Memory Aid A and unsolicited adverse events (AEs) that occurred from Day 0 through Day 28 on Memory Aid B. Serious adverse events (SAEs) and medically-attended events (MAEs) were collected for six months following vaccination.

Reviewer comment: Randomization was not stratified according to age group, however, in order to ensure balanced enrollment across age and treatment groups, the sponsor used an Interactive Voice Response System (IVRS) programmed to cap enrollment to the entire study, each site, and to each of three age groups: 50-64, 65-74, and ≥75 years of age. The SAP clarified that randomization was performed using traditional computer-generated statistical methods and that the IVRS was used as a secondary method to achieve a balanced age stratification. The system is an automated telecommunication tool that is capable of inputing clinical trial data. It can also be used to recruit and register subjects for clinical trials. For example, a potential participant calls a toll-free number, answers a series of questions to determine eligibility, and, if eligible, is entered into a central database. Study personnel are then alerted to call the potential subject. The statistical reviewer found the randomization and blinding procedures acceptable. Please see the statistical review for further discussion.

Reviewer comment: The SAP for PSC12 included a blinded interim analysis of the number of cases of rt-PCR-confirmed ILI at the end of the first influenza season. The Applicant calculated a pre-defined number of cases that would be sufficient to demonstrate the NI of Flublok Quadrivalent without having to extend the study to a second season. The statistical reviewer agreed with the Applicant's assessment that adjustment of the type 1 error (alpha) was not necessary because the analysis involved a blinded enumeration of accrued cases of rt-PCR-confirmed ILI with no hypothesis testing.

Reviewer comment: Although the Applicant reported that five study sites were identified for the immunogenicity subset prior to initiating the study, the statistical reviewer found that, for two of the five study sites, instead of including all subjects in the Immunogenicity Population according to the protocol, only 29.1% and 19.6% (Sites 34 and 37, respectively) of subjects in the Randomized Population were included in the IP. In response to an IR (STN 125285/194.19), the Applicant explained that, consistent with the study protocol and SAP, only three sites (Sites 10, 14, and 39) were pre-selected for inclusion in the immunogenicity subset. Because it appeared that these sites might not fully enroll the immunogenicity subset, two additional sites were asked to participate, and as of November 7, 2014 and November 13, 2014, all subsequently randomized subjects at Sites 34, and 37, respectively, were included in the immunogenicity subset. The statistical reviewer noted that the immunogenicity subset design and analyses were limited because subjects were not selected randomly or stratified by study site. However, because the immunogenicity analyses were secondary and descriptive, and results were not included in the Package Insert, the clinical and regulatory impact of the results are limited. Please see the statistical review for further comment.

6.2.3 Population

Selected Inclusion Criteria

- Ambulatory, "medically stable" (as determined by medical history and targeted exam and defined as "no change in diagnoses or chronic medications, dose or class, for medical reasons in the 3 months prior to study") adults 50 years of age and older.

Selected Exclusion Criteria

- Known contraindication to either study vaccine per package inserts.
- Receipt of any other influenza vaccine within 180 days prior to enrollment.
- Disease or therapy that may cause immunocompromised.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Group A: Flublok Quadrivalent containing a total of 180mcg recombinant hemagglutinin (rHA), 45mcg per each of four antigens derived from influenza A/H1N1, A/H3N2, B Yamagata, and B Victoria viruses, in a total volume of 0.5mL, provided in pre-filled syringes. Stored in a sodium phosphate buffer with 0.005% Tween-20. Batch #QFCA1401.

Group B: US-licensed IIV4 (Fluarix Quadrivalent) containing a total of 60mcg of influenza hemagglutinin, 15 mcg per each of four antigens derived from influenza A/H1N1, A/H3N2, B Yamagata, and B Victoria viruses, in a total volume of 0.5mL, provided in pre-filled syringes. Lot#GA22N.

Each study vaccine contained antigens derived from the four influenza strains (or "like viruses") recommended by the VRBPAC for inclusion in quadrivalent vaccines for the US 2014-2015 season (shown in Table 24):

Table 24: Influenza Virus Strains Included in PSC12 Study Vaccines

Strain	Flublok RIV4	Fluarix QIV
A/H1N1	A/California/07/2009	A/Christchurch/16/2010*
A/H3N2	A/Texas/50/2012	A/Texas/50/2012
B/Yamagata lineage	B/Massachusetts/2/2012	B/Massachusetts/2/2012
B/Victoria lineage	B/Brisbane/60/2008	B/Brisbane/60/2008

Source: Adapted from STN 125285/194, Module 5, CSR PSC12, p.11.
*An A/California/07/2009-like virus

Each subject received a single 0.5mL dose of assigned study vaccine administered intramuscularly (IM) in the deltoid region of the upper arm.

6.2.5 Directions for Use

Not applicable.

6.2.6 Sites and Centers

Table 25 presents a list of each study site, principal investigator, and number of subjects.

Table 25: Study Sites, Investigators, and Subjects* - PSC12

Site	Investigator	Location	#Subjects*
10	George Bauer, MD	Metairie, LA	175
11	James Borders, MD	Lexington, KY	248
12	Paul Bradley, MD	Savannah, GA	281
13	James Cervantes, MD	Bellevue, NE	72
14	Laurence Chu, MD	Austin, TX	148
15	Enrique Cifuentes, MD	Tempe, AZ	252
16	Lisa Connery, MD	Norman, OK	131
17	Matthew Davis, MD	Rochester, NY	302
18	William Douglas, MD	Sacramento, CA	227
19	David Ensz, MD	Dakota Dunes, SD	75

Site	Investigator	Location	#Subjects*
20	Robert Epstein, MD	San Francisco, CA	224
21	John Ervin, MD	Kansas City, MO	308
22	Brandon Essink, MD	Omaha, NE	173
23	Carl Griffin, MD	Oklahoma City, OK	184
24	Darrell Herrington, MD	San Angelo, TX	151
25	Jeffry Jacqmein, MD	Jacksonville, FL	226
26	Holly Dushkin, MD, Alan Kravitz, MD	Cleveland, OH	374
27	Kurt Lesh, MD	Colorado Springs, CO	143
28	Michael McCartney, MD	Methuen, MA	169
29	Emmanuel Miel, MD	Jacksonville, FL	145
30	Jerome V. Mirkil, MD	Las Vegas, NV	219
31	Derek Muse, MD	Salt Lake City, UT	332
32	Suchet Patel, MD	Endwell, NY	299
33	Eric Bravo, MD	Little Rock, AR	277
34	Terry Poling, MD	Wichita, KS	301
35	Bruce Rankin, DO	DeLand, FL	342
36	Demetrius Rizos, DO	Newington, NH	179
37	Jeffrey Rosen, MD	Coral Gables, FL	244
38	Jamshid Saleh, MD	Redding, CA	220
39	William Seger, MD	Fort Worth, TX	174
40	Stephan Sharp, MD	Nashville, TN	224
41	Harry Studdard, MD	Mobile, AL	315
42	Mark Turner, MD	Meridan, ID	295
43	Treva Tyson, MD	Raleigh, NC	218
44	Susann Varano, MD	Milford, CT	111
45	Keith Vrbicky, MD	Norfolk, NE	106
46	Alexander White, MD	Port Orange, FL	276
47	Duane Wombolt, MD	Norfolk, VA	260
48	Richard Mills, MD	Mount Pleasant, SC	167
49	Jonathan Wilson, MD	Winston-Salem, NC	130

Source: Adapted from STN 125285.194, PSC12 CSR, Appendix 16.1.4 and electronic datasets.
*Number of subjects in the Safety Population

6.2.7 Surveillance/Monitoring

Table 26 presents the schedule of procedures for PSC12.

Table 26: Study Procedures – PSC12

Visit	**1**	**2 Phone**	**2a IVRS**	**Biweekly Phone**	**3[1]**	**Unscheduled Visit**	**Early Exit**
Day (window)	**0**	**8-10[1]**	**Twice Weekly 0-180[2]**	**Day 0 to EOIS (+/- 3days)[1]**	**28[1] (28-36)**	**ILI visit[3] (<72hrs after onset)**	**--**
Informed consent	X	--	--	--	--	--	--
Eligibility criteria	X	--	--	--	--	--	--
Medical history	X	--	--	--	--	X	X
ILI symptoms		--	X[2]	X[1]	--	X	--
Targeted physical exam[4]	X	--	--	--	--	X	X
Temperature	X	--	--	--	--	X	X
Vaccination	X	--	--	--	--	--	--
Flu symptom card review	--	--	--	--	--	X	--
SAE/MAE review	X	X[1]	--	X[1]	X[1]	X	X
Unsolicited AEs[5]	X	X[1]	--	--	X[1]	--	--
Memory Aid A review	--	X[1]	--	--	--	--	--
Concomitant meds[6]	X	--	--	X[1]	--	X	X
Serologies[7]	X[7]	--	--	--	X[7]	--	--

Visit	**1**	**2 Phone**	**2a IVRS**	**Biweekly Phone**	**3[1]**	**Unscheduled Visit**	**Early Exit**
Day (window)	**0**	**8-10[1]**	**Twice Weekly 0-180[2]**	**Day 0 to EOIS (+/- 3days)[1]**	**28[1] (28-36)**	**ILI visit[3] (<72hrs after onset)**	**--**
NP swab for virus detection	--	--	--	--	--	X	--
Memory Aids reviewed[8]	--	--	--	--	X[8]	--	X[8]

Source: Adapted from STN 125285/194, Module 5, PSC12 CSR, Table 15.
[1]Phone contact on Day 8-10 and every 2 weeks until the end of the influenza season (EOIS) to review AEs, SAEs, MAEs, and ILIs. Subjects were also contacted by phone or other electronic means if they failed to make their twice weekly Interactive Voice Response System (IVRS) call. Visit 3, Day 28, was a clinic visit only for subjects in the pre-selected serology subset.
[2]Calls from subject to IVRS system throughout the study.
[3]Reporting of ILI symptoms began immediately after vaccination
[4]Targeted exam included vital signs, oropharynx, skin, heart, lungs, and cervical, axillary, and epitrochlear lymph nodes.
[5]All unsolicited AEs through Day 28
[6]After Day 28, only concomitant medications associated with treatment of SAEs/MAEs or influenza disease were collected.
[7]HI serologies performed on all subjects at five preselected sites
[8]Memory Aid A (solicited AEs) was reviewed and returned for maintenance with source documents on Day 28 at which time subjects were reminded to complete and return Memory Aid B (unsolicited AEs, SAEs, MAEs) at the end of the study (i.e., between 6 and 8 months post-vaccination).

Reviewer comment: PSC12 CSR Table 15, p.39, and the study protocol stated that 2-3 study sites were pre-selected for the immunogenicity subset while the remainder of CSR, tables, and datasets indicated that 5 study sites were pre-selected for immunogenicity (Sites 10, 14, 34, 37, and 39). Please see Section 6.2.2, Design Overview for the Applicant's clarification submitted in a response to an IR (STN 125285/194.19) regarding this issue.

After collection of baseline HI serologies on Day 0, all subjects received a single 0.5mL dose of study vaccine administered intramuscularly. Subjects in the immunogenicity subset returned to the study site on Day 28 for post-vaccination HI titers. Telephone and other electronic follow-up and return visits for AEs and/or ILI evaluations were as outlined in Table 26.

Surveillance for Influenza-Like Illness (ILI)

Surveillance for ILI was both active and passive. Subjects were instructed to call the IVRS twice weekly to report whether they experienced pre-specified respiratory or systemic symptoms that might define ILI. If such symptoms occurred, subjects were to call the study site immediately, complete a Flu Symptom Card, and return to the study site as soon as possible, and no later than 72 hours following onset of ILI symptoms, for evaluation and virologic testing. The study site actively contacted subjects if the IVRS reported that they missed their twice-weekly phone calls. Study personnel also actively contacted subjects at least once every two weeks until the end of the influenza season (EOIS) both to elicit flu symptoms and to remind subjects to record AEs, medications, and follow other study procedures.

The ILI visit included a medical evaluation and nasopharyngeal (NP) swab for viral rt-PCR. Aliquots of the NP swab sample were reserved for culture of rt-PCR-positive samples. The Flu Symptom Card was also reviewed at this visit for protocol-defined ILI

which included at least one respiratory symptom accompanied by at least one systemic symptom presented in Table 27:

Table 27: Protocol Defined Influenza-Like Illness (ILI) – PSC12

Respiratory Symptoms	Systemic Symptoms
Sore throat	Fever >37.2°C (>99.0°F)
Cough	Chills (shivering)
Sputum production	Tiredness (fatigue)
Wheezing	Headache
Difficulty breathing	Myalgia (muscle ache)

Source: Adapted from STN 125285/194, Module 5, PSC12 CSR, p.40.

Reviewer comment: Protocol-defined ILI was less specific but more sensitive than the CDC's U.S. outpatient surveillance system definition of ILI: fever (temperature of 100°F [37.8°C] or greater) AND a cough and/or a sore throat without a known cause other than influenza. The definition was acceptable for the purposes of this study in terms of capturing all potential cases of laboratory-confirmed influenza and because elderly patients may be less likely to mount a febrile response to infections than younger individuals.

Definitions and Criteria for the Assessment of Severity and Causality of AEs

Definitions of AEs and SAEs were consistent with those in 21 CFR 312.32. AEs were followed to resolution or stabilization. MAEs were defined as events leading to a visit to or from medical personnel for any reason, including emergency department (ED) visits. Telephone contact with a healthcare professional was not considered a MAE. If a MAE met SAE criteria, it was also reported as an SAE.

Solicited local and systemic AEs and the scale for grading the severity of these events are presented in Table 28:

Table 28: Toxicity Grading Scale for Solicited Local and Systemic Reactogenicity – PSC12

Injection site Reaction	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Pain	Does not interfere with activity	Interferes with activity	Prevents daily activity	Requires hospitalization or ER visit
Tenderness	Does not interfere with activity	Interferes with activity	Prevents daily activity	Requires hospitalization or ER visit
Erythema/redness	25 to ≤50mm Small	51 to ≤100mm Medium	>100mm Large	Necrosis or exfoliative dermatitis
Induration/firmness	25 to ≤50mm Small	51 to ≤100mm Medium	>100mm Large	Necrosis
Systemic Reactogenicity	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Chills Fatigue/malaise Myalgia Joint ache Headache Nausea	No interference with activity	Some interference with activity	Significant interference with activity, prevents daily activity	ER visit or hospitalization
Body temperature	100.4-101.1°F	101.2-102.0°F	102.1-104.0°F	>104.0°F

Source: Adapted from STN 125285/194, Module 5, Volume 10, PSC12 Protocol, pp.43-44.

The toxicity grading scale for unsolicited AEs is presented in Table 29:

Table 29: Toxicity Grading Scale for Unsolicited Adverse Events – PSC12

Grade	Definition
Grade 1-Mild	Causing no limitation of usual activity
Grade 2-Moderate	Causing some limitation of usual activity
Grade 3-Severe	Causing inability to carry out usual acitivities
Grade 4-Life-threatening	Required hospitalization or ER visit

Source: Adapted from STN 125285/194, Module 5, Volume 10, PSC12 Protocol, p.43.

Criteria for the Assessment of Causality of Unsolicited AEs

- Not related: Events clearly considered due to extraneous causes (pre-existing or known medical condition, concomitant medication, environmental factor, etc.) unrelated to a study product. It can be readily explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
- Related: All AEs were considered related if they were not assessed as non-related.

Reviewer comment: Solicited AEs were similar to those collected in previous clinical studies of Flublok and were events commonly reported in other adult influenza vaccine trials. The toxicity grading scale for solicited AEs was similar to that used in PSC16 except that the criteria used in PSC12 did not consider the use of medications to relieve symptoms. The toxicity grading scales for unsolicited AEs in PSC12 and PSC16 were very similar. Criteria used to assess causality in PSC12 and PSC16 were identical.

Halting Rules and Data Monitoring Committee (DMC)

Criteria for suspending enrollment pending review by the DMC were as follows:

- Incidence of severe (Grade 3 or 4) reactogenicity notably higher than described in the study vaccine package inserts, as determined by the Medical Monitor; or
- Three or more SAEs of the same type considered unexpected and related to study vaccine.

Halting rules were not triggered during the study.

6.2.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

rt-PCR-confirmed, protocol-defined ILI caused by any influenza strain that began at least 14 days post-vaccination was the primary study endpoint and was tabulated by treatment group. Relative vaccine efficacy (rVE) was calculated as:

$rVE = 1- RR = 1 - (\text{Attack Rate}_{\text{Flublok RIV4}} / \text{Attack Rate}_{\text{IIV4}})$

Non-inferiority was established if the lower bound (LB) of the two-sided 95% CI for rVE was greater than the NI margin of –0.20.

Secondary Efficacy Endpoints

Secondary efficacy endpoints included rVE measured by other case definitions as follows:

- rt-PCR-confirmed CDC-defined ILI that begins at least 14 days post-vaccination caused by any influenza strain.
- Culture-confirmed protocol-defined ILI that begins at least 14 days post-vaccination caused by an influenza strain (identified from the same clinical sample) antigenically matched to those represented in the study vaccines.
- Culture-confirmed CDC-defined ILI that begins at least 14 days post-vaccination caused by an influenza strain (identified from the same clinical sample) antigenically matched to those represented in the study vaccines.

Reviewer comment: Because of its greater sensitivity, rt-PCR rather than viral culture was used to confirm influenza as the cause of ILI. PCR-positive samples were then cultured to isolate virus for antigenic identification. rt-PCR is a common accepted method of identifying influenza cases in clinical endpoint trials and CDC surveillance studies of influenza.

Secondary Immunogenicity Endpoints

Pre- (Day 0) and post-vaccination (Day 28) HI GMTs and SCRs for all four antigens in a subset of ~520 subjects (subjects from five pre-selected study sites) were compared between treatment groups. GMT ratios and differences in SCRs were calculated and evaluated according to the following success criteria for non-inferior immunogenicity:

- The upper bound (UB) of the two-sided 95% CI on the difference between SCRs ($SCR_{IIV4} - SCR_{Flublok\ RIV4}$) must not exceed 10%.
- The UB of the two-sided 95% CI on the GMT ratio ($GMT_{IIV4} / GMT_{Flublok\ RIV4}$) must not exceed 1.5.

Non-inferior immunogenicity was concluded for the entire age spectrum if the success criteria were met.

Secondary Safety Endpoints

- The incidence and maximum severity of solicited local injection site and systemic reactogenicity as recorded on Memory Aid A from Day 0 through Day 7, summarized using descriptive statistics. Denominators for each parameter included all subjects for whom any data was provided during the 7 day monitoring period. Subjects for whom all 7 days of data for a given parameter were missing, were excluded from the denominator for that parameter. The sponsor planned to conduct an exploratory sensitivity analysis for solicited AEs in which a severity grade of "severe" would be imputed for missing severity data.
- The incidence, severity, and relatedness of unsolicited treatment-emergent AEs (TEAEs) reported in the 28 days following vaccination (Day 0 through Day 28), categorized by MedDRA system organ class (SOC) and preferred term (PT), summarized using descriptive statistics. AEs were considered treatment-emergent if they began after vaccination on Study Day 0. Subjects were counted once per PT and per SOC, and once per maximum intensity for each category, and once by closest relationship to study vaccine.
- SAEs and MAEs occurring from Day 0 through the EOIS (at least 6 months post-vaccination) were listed.

Reviewer comment: The use of an active U.S.-licensed comparator rather than a placebo and the assessment of non-inferior efficacy and immunogenicity were acceptable for an influenza vaccine trial in a population for whom annual influenza vaccination is recommended.

Exploratory Analyses

- Sub-analyses of non-inferior rVE and immunogenicity were conducted according to age subsets, sex, race, ethnicity, and previous vaccine history.
- Sub-analyses of solicited, unsolicited, and SAEs were conducted according to age subsets, sex, race, and ethnicity.

Exploratory Analysis of Superior Vaccine Efficacy

Sections 1.15.1.1 and 11.8 of the study protocol (version 1.1) stated that if the primary endpoint of non-inferior VE was demonstrated, relative VE would be tested for superiority as an exploratory analysis. Superior VE of Flublok relative to IIV4 was pre-specified as a LB of the two-sided 95% CI of rVE > 9%.

Reviewer comment: Although the exploratory analysis of superiority was pre-specified in the study protocol, it was not described in the statistical considerations section of the CSR and was not pre-specified in the SAP. In an Advice and Information Request regarding IND 15784 Amendment 15, dated July 1, 2014, CBER informed PSC that we considered an analysis of superior VE exploratory and that claims of superiority would not be included in the Flublok label (PSC12, item 3.f).

6.2.9 Statistical Considerations & Statistical Analysis Plan

Please see the statistical review for a complete discussion of the statistical analysis plan.

Hypothesis

The primary analysis was a test of the non-inferior efficacy of Flublok relative to IIV4 in the prevention of rt-PCR-confirmed protocol-defined ILI due to any influenza strain in subjects randomly assigned to receive Flublok or IIV4.

- Null hypothesis: H_0: Relative VE < -0.20
- Alternative hypothesis: H_A: Relative VE ≥ -0.20
- Where:
    - M=margin of difference used to define non-inferiority = -0.20
    - AR_F=attack rate for Flublok RIV4
    - AR_{IIV4}=attack rate for IIV4
    - RR=relative risk, the ratio of attack rates = AR_F / AR_{IIV4}
    - Relative VE = 1 – RR

Study Endpoints – Please see Section 6.2.8.

Sample Size

The sponsor calculated that a sample size of 4311 per group was required to demonstrate NI with 80% power assuming true attack rates of 2% for IIV4, 1.53% for Flublok RIV4, and a one-sided alpha level of 0.025. To allow for an attrition rate of ~4-5%, the sponsor proposed a sample size of 4500 per group (total n=9000). The sponsor calculated that a total of 153 cases would be sufficient to demonstrate non-inferior relative vaccine efficacy.

Reviewer comment: Based on previous clinical trial data, the assumptions of true attack rates between 1-2% were reasonable. The attack rate for influenza is variable and could be higher or lower in any given year. The sponsor provided references to support their assumptions and agreed to extend the study to a

second season if attack rates were not sufficient to support their hypothesis in the first season.

6.2.10 Study Population and Disposition

The first subject was enrolled on October 22, 2014; the last subject completed the study on May 22, 2015. Nasopharyngeal swabs for ILI were collected from October 30, 2014 through April 23, 2015 (EOIS).

6.2.10.1 Populations Enrolled/Analyzed

Analysis populations were defined as follows:

- Efficacy Population (EP): The EP was used for all analyses of efficacy and included all randomized subjects who received study vaccine and provided any follow-up documentation for ILI beginning at least 14 days after vaccination. The EP excluded subjects with protocol deviations that could adversely affect efficacy. Decisions to exclude subjects from the EP were documented and finalized prior to unblinding the study.
- Immunogenicity Population (IP): The IP included all randomized subjects who received a dose of study vaccine, provided serum samples for Day 0 and Day 28 HI titers, and had no major protocol deviations that might adversely affect the immune response. Deviations that would result in exclusion from the IP were determined prior to database lock and unblinding the study.
- Safety Population (SP): The SP included all subjects who received a dose of study vaccine for any evaluable safety data were available after vaccination.
- Reactogenicity Population (RP): The RP included all subjects who received known study vaccine and provided data on at least one day of the 7-day Memory Aid A for a given category of reactogenicity event. There were three reactogenicity subpopulations:
    - RP A: Subjects with ≥1 injection site reaction recorded in Memory Aid A.
    - RP B: Subjects with ≥1 systemic reaction recorded in Memory Aid A.
    - RP C: Subjects with ≥1 body temperature recorded in Memory Aid A.

Subjects were analyzed according to actual treatment received in all three analysis populations.

<u>Changes in the Conduct of the Study or Planned Analyses</u>

The sponsor states that no changes were made to the conduct of the study but that the following changes were made to the original SAP:

- CDC-ILI was defined as an ILI accompanied by fever.
- The summary of SAEs and MAEs was changed to a summary according to MedDRA PT and SOC.
- The Applicant stated that cultures of influenza from rt-PCR-positive nasopharyngeal (NP) swabs could not be processed to generate adequate titers of viruses to test against ferret antiserum for antigenic identification. Therefore, secondary analyses of rVE for ILI due to strains that matched the strains included in the study vaccines were not performed.

Reviewer comment: In response to an IR (STN 125285/194.20), PSC explained that, due to a miscommunication between contract laboratories, rt-PCR-positive NP swabs that subsequently grew in viral culture were mistakenly discarded instead of forwarded to another laboratory for antigenic characterization. The Applicant states that, because the 2014-2015 influenza season was characterized

by a predominance (>80%) of circulating viruses that were not antigenically matched to the vaccine strains, the ability to conduct analyses of rVE according to matched strains would not have provided significant information regarding the clinical efficacy of Flublok RIV4. This assumes that sampling from national surveillance closely reflected the epidemiology of viruses circulating in study site locations. VE is dependent on antigenic similarity between circulating virus strains and vaccine virus antigens. Differences in the degree of antigenic similarity to circulating strains between the egg-based and recombinant study vaccines might translate into differences in VE. The inability to evaluate rVE against documented matched strains is a limitation of the study. However, the reviewer agrees that it is reasonable to assume that the antigenic similarity of the study isolates reflected CDC surveillance.

Interim Analyses, Data Monitoring

Prior to the database lock and unblinding, the total number of cases of rt-PCR-confirmed protocol-defined ILI was quantified to assure that an adequate number of cases were accumulated to yield useful information in the by-treatment analysis.

Individual SAEs were reviewed by the PSC Medical Monitor as they were reported. None were judged as related to study vaccine by the investigators or the Medical Monitor. Only one subject was unblinded prior to the database lock and completion of the study due to an SAE of death attributed to cocaine intoxication.

6.2.10.1.1 Demographics

Table 30 presents demographics and baseline characteristics of all subjects with post-randomization data (Safety Population) according to treatment group. Distribution across treatment groups was balanced. The mean age of subjects was 62.7 years in the Flublok RIV4 group and 62.6 years for IIV4. Females, white/Caucasians, and non-Hispanics comprised the majority of the study population (58.4%, 80.2%, and 95.1%, respectively).

Table 30: Demographics and Baseline Characteristics – PSC12 (Safety Population)

Characteristic	**Flublok RIV4 N=4328**	**IIV4 N=4344**	**US Census (July 2014)****
Mean Age (yrs)	62.7	62.6	--
Median Age	61.0	61.0	--
Min, Max Age	50, 96	50, 94	--
Age group, n(%)	--	--	--
50-64	2569 (59.4)	2617 (60.2)	--
≥65	1759 (40.6)	1727 (39.8)	14.5%
65-74	1234 (28.5)	1254 (28.9)	--
≥75	525 (12.1)	473 (10.9)	--
Gender – Male, n(%)	1796 (41.5)	1807 (41.6)	49.2%
Gender – Female, n(%)	2532 (58.5)	2537 (58.4)	50.8%
Race, n(%)	--	--	--
American Indian/Alaska Native	36 (0.8)	40 (0.9)	1.2%
Asian	17 (0.4)	18 (0.4)	5.4%
Black/African American	773 (17.9)	753 (17.3)	13.2%
Native Hawaiian/Pacific Islander	5 (0.1)	12 (0.3)	0.2%
White/Caucasian	3467 (80.1)	3493 (80.4)	77.4%
Other	30 (0.7)	28 (0.6)	--

Characteristic	Flublok RIV4 N=4328	IIV4 N=4344	US Census (July 2014)**
Ethnicity, n(%)	--	--	--
Hispanic/Latino	206 (4.8)	219 (5.0)	17.4%
Non-Hispanic/Latino*	4122 (95.2)	4123 (94.9)	82.6%
Influenza vaccination in previous season	2311 (53.4)	2340 (53.9)	--

Source: STN 125285/194, Module 5, PSC12 CSR, Table 14.1.3.1
*Two subjects in the IIV4 group had missing ethnicity data.
** US census data as of July 1, 2014 accessed on February 29, 2016 at http://www.census.gov/popest/data/
Total US population=318,857,056. Adults 18-64 yrs=199,030,227. Adults ≥65 yrs=46,243,211. Male=156,936,487. Female=161,920,569. White=246,660,710. Black/African American=42,158,238. American Indian/Alaskan Native=3,960,971, Asian=17,339,053. Native Hawaiian/Pacific Islander=741,601. ≥two races=7,996,483. Non-Hispanic/Latino=263,469,517. Hispanic/Latino=55,387,539.

Reviewer comment: Females and blacks/African Americans were somewhat overrepresented while Asians and Hispanics/Latinos were underrepresented relative to the U.S. population.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Influenza Vaccination History

Of 8672 subjects in the Safety Population, 4651 (53.6%) reported having received an influenza vaccine in the previous season (Flublok RIV4 53.4%, IIV4 53.9%).

Medical History

The most common pre-existing conditions among all subjects in the Safety Population involved the following categories of disorders: cardiovascular (99.1%); musculoskeletal system (88.5%); genital/reproductive (59.9%); allergies (57.0%); head and neck (55.8%); gastrointestinal (52.4%); metabolic/endocrine (45.9%); surgical (32.2%); psychiatric (32.0%); nervous system (24.8%); and pulmonary (18.6%). The proportion of subjects with a history of autoimmune or immunodeficiency disorders was small (0.6% and 1.3%, respectively). The majority of immunodeficiency disorders consisted of remote history of shingles, cold sores/oral herpes, and various environmental, drug, or food allergies. There were a few subjects with prior history of collagen vascular diseases (e.g., lupus, rheumatoid arthritis, polymyalgia rheumatica), and two subjects in the IIV4 group who were infected with the human immunodeficiency virus (HIV). Autoimmune diseases were varied, with rheumatoid arthritis being the most common condition reported by eight subjects.

Reviewer comment: Overall, the different types of pre-existing medical conditions were balanced between treatment groups.

Concomitant Medications

A total of 84% of subjects in each treatment group reported taking concomitant medications at enrollment. Steroid use was topical or inhaled according to protocol. Five subjects (two Flublok RIV4 and three IIV4 recipients) were taking immunosuppressive agents for collagen vascular diseases (azothiaprine, golimumab, etanercept, and infliximab) at the time of vaccination.

Reviewer comment: Concomitant medications were typical of an older adult and elderly population. The number of subjects on immunosuppressive medications was low with medication classes balanced between treatment groups, and should not have biased interpretation of study results.

6.2.10.1.3 Subject Disposition

Table 31 presents the disposition of subjects and analysis populations for PSC12.

Table 31: Subject Disposition and Analysis Populations, All Subjects ≥50 Years – PSC12 (Randomized Population)

Disposition	Flublok RIV4 N=4474 n(%)	IIV4 N=4489 n(%)
Randomized Population[1]	4474	4489
Efficacy Population	4303 (96.2)	4301 (95.8)
Immunogenicity Population	317 (7.0)	300 (6.7)
Safety Population	4328 (96.7)	4344 (96.8)
Reactogenicity Population	4312 (96.4)	4327 (96.4)
-Reactogenicity Population A[2]	4307 (96.3)	4319 (96.2)
-Reactogenicity Population B[3]	4306 (96.2)	4318 (96.2)
-Reactogenicity Population C[4]	4262 (95.3)	4282 (95.4)
Completed Study	4228 (94.5)	4236 (94.4)
Primary Reason for Early Withdrawal	--	--
-adverse event	9 (0.2)	8 (0.2)
-investigator decision	1 (0.0)	2 (0.0)
-lost to follow-up	176 (3.9)	172 (3.8)
-sponsor request	0	0
-withdrawal of consent unrelated to AE	53 (1.2)	61 (1.4)
-other	7 (0.2)	10 (0.2)

Source: STN 125285/194, Module 5, PSC12 CSR Tables 16 and 14.1.1
[1]Excludes 40 randomized subjects who either withdrew prior to vaccination (n=15) or for whom the vaccine received could not be verified (n=25; 12 assigned to Flublok RIV4; 13 assigned to IIV4).
[2]Subjects with any injection site reactogenicity data, Days 0-7.
[3]Subjects with any systemic reactogenicity data, Days 0-7.
[4]Subjects with any body temperature data, Days 0-7.

Of 9003 subjects enrolled and randomized, 8988 received a dose of study vaccine. Fifteen subjects withdrew prior to vaccination and were not included in any analyses. An additional 25 subjects (12 assigned to Flublok RIV4 and 13 assigned to IIV4) at Site 44 received a dose of vaccine the identity of which could not be verified from site records and were also excluded from the final analysis.

At CBER's request, the sponsor reported rates of completion and return of Memory Aids A and B for recording solicited and unsolicited AEs, respectively (data not shown, see PSC CSR Tables 14.1.1 and 14.1.2.1). Among the Randomized Population, the proportions of subjects in the Flublok RIV4 and IIV4 groups who completed Memory Aid A were 95.7% and 95.8%, respectively, and, for Memory Aid B, 91.6% and 91.7%, respectively.

Reviewer comment: Subject disposition was balanced between treatment groups. A total of 8464 (96.4%) randomized and vaccinated subjects in the final analysis completed the study. The early withdrawal rate, primarily due to lost to follow-up (3.9%) or voluntary withdrawal of consent (1.3%), was low, similar between treatment groups, and should not have influenced interpretation of study results. Withdrawal due to AEs was low (0.2%). Compliance with documenting AEs on the Memory Aids (91.6%-95.8%) was good. Evaluation of the electronic datasets was consistent with the sponsor's report.

Reviewer comment: BiMO did not investigate Site 44, where site records could not verify actual treatment received for 25 subjects, for inspection. However, withdrawal of these subjects from the final analysis was balanced with regard to assigned treatment and should not have significantly impacted interpretation of study results.

Major protocol deviations for the Randomized Population are summarized in Table 32. Most deviations were due to missing a study visit and/or providing laboratory samples.

Table 32: Protocol Deviations – PSC12 (Randomized Population)

Deviation Category	Flublok RIV4 N=4474 n(%)	IIV4 N=4489 n(%)
Subjects with any major protocol deviation[1]	124 (2.8)	127 (2.8)
-Concomitant medication	0	1 (0.0)
-Dosing error	3 (0.1)	5 (0.1)
-Exclusion criteria	0	1 (0.1)
-Lab sample	28 (0.6)	27 (0.6)
-Missed study visit	41 (0.9)	36 (0.8)
-Procedure not per protocol	36 (0.8)	42 (0.9)
-Unblinding	1 (0.1)	0
-Visit out of window	6 (0.1)	4 (0.1)
-other	11 (0.2)	13 (0.3)
Subjects with any major protocol deviation for immunogenicity[2]	24 (0.5)	25 (0.6)
-Lab sample	3 (0.1)	2 (0.0)
-Missed study visit	23 (0.5)	24 (0.5)
-Procedure not per protocol	1 (0.0)	0
-Visit out of window	0	1 (0.0)

Source: STN 125285/194, PSC12 CSR, Module 5, Table 14.1.2.2.
[1]Excluded from Efficacy and Immunogenicity Populations
[2]Excluded from Immunogenicity Population

Reviewer comment: The rates of protocol deviations leading to exclusion from the efficacy and/or immunogenicity analyses were low overall, balanced between treatment groups, and unlikely to influence the overall interpretation of study results.

6.2.11 Efficacy Analyses

6.2.11.1 Analysis of the Primary Endpoint

The primary endpoint analysis was based on the relative risk of rt-PCR-confirmed protocol-defined ILI caused by any influenza virus strain in the Efficacy Population. Results of the primary endpoint analysis are presented in Table 33:

Table 33: Relative Vaccine Efficacy of rt-PCR-Confirmed ILI Due to All Influenza Virus Strains – PSC12 (Efficacy Population)

Flublok RIV4 N=4303	Flublok RIV4 N=4303	IIV4 N=4301	IIV4 N=4301	RR	rVE (95% CI)
n (#of cases)	Attack Rate	n (# of cases)	Attack Rate	$AR_{Flublok}/AR_{IIV4}$	(1 - RR) x 100
96	2.2	138	3.2	0.70	30% (10%, 47%)

Source: STN 125285/194.9, Module 5, PSC12 CSR, Table 14.2.1.1(03Mar2016).
Attack Rate (AR) = # of cases of ILI / # subjects in the treatment group
Relative Risk (RR) = AR Flublok RIV4 / AR IIV4
Relative Vaccine Efficacy (rVE) of Flublok RIV4 versus IIV4 = (1 – RR) x 100

Flublok RIV4 met pre-specified success criteria for non-inferior vaccine efficacy relative to IIV4, i.e., that the LB of the 95% CI of relative efficacy must be greater than –20%. This effect became apparent at ~4 weeks post-vaccination and persisted through the influenza season (through ~Day 196) [data not shown, please see PSC12 CSR, Figure 1, p.51.]

The Applicant reported that the primary analysis excluded four subjects (three IIV4 recipients and one Flublok RIV4) who were hospitalized with documented influenza (and reported as SAEs).

Reviewer comment: Exclusion of three IIV4 and one Flublok RIV4 recipient from the Efficacy Population should not have significantly impacted the interpretation of efficacy results and, if anything, may have favored IIV4 in the rVE analysis by lowering the attack rate for IIV4.

Reviewer Comment: As noted in Section 6.2.10.1, the sponsor reported that they were unable to determine antigenic similarity or matching to vaccine virus strains. However, based on CDC surveillance from the 2014-2015 influenza season, influenza A/H3N2 was the predominant circulating virus until late February 2015, and the majority of circulating wildtype influenza A/H3N2 virus strains were antigenically dissimilar or mismatched relative to the vaccine strain. The CDC estimated the vaccine effectiveness of inactivated influenza vaccines (without specifying specific brands) in preventing medically-attended outpatient rt-PCR-confirmed influenza illness in the US using a prospective case-positive test negative control design (TND) observational study. End of season vaccine effectiveness estimates through April 10, 2015 reflected predominant B/Yamagata viruses from the end of February through April 2015, and were as follows: 23% (95% CI: 14%, 31%) for all A and B viruses, all ages; 13% (95% CI: 2%, 23%) for A/H3N2, all ages. End of season vaccine effectiveness estimates against A/H3N2 by age subgroup were not published but were presented to the ACIP in June 2015. The point estimates for vaccine effectiveness against A/H3N2 for adults 18-49 years, 50-64 years, and ≥65 years were -2%, 19%, and 17%, respectively. The LBs of the 95% CIs for adults 18-49 years, 50-64 years, and ≥65 years, were approximately -30%, -10%, and -25%, respectively (bar graph). Surveillance data and case-control TND observational studies conducted in Canada and the United Kingdom (UK) during the 2014-2015 influenza season found a similar antigenic mismatch for A/H3N2 and very low overall estimates of vaccine effectiveness with 95% CIs that included zero. Although limited, TND observational studies have been shown to correlate well with randomized placebo-controlled trials. In this reviewer's opinion, the VE of Flublok RIV4 relative to Fluarix RIV4 in a season characterized by a predominant antigenically mismatched influenza A/H3N2, where overall vaccine effectiveness estimates were very low, is difficult to interpret as a clear success because the study product was non-inferior to a vaccine whose performance, based on CDC surveillance, was probably very poor and lower than expected. The validity of a non-inferiority study depends on a comparator that performs as expected. Nevertheless, we can also view the results of PSC12 as demonstrating that Flublok RIV4 was more efficacious during a season of antigenic mismatch which is a more difficult threshold to reach than when a vaccine is well-matched to circulating strains. Although the Applicant declined our recommendation to extend PSC12 to a second season because of the unexpectedly low vaccine effectiveness for the 2014-2015 season (the 2015-

2016 season has been characterized by well-matched predominant A/H1N1 and B viruses and may have provided more definitive data), data from PSC12 support approval. [15,16,18,23,59,61,71,79]

Regarding available clinical trial data specific to the Fluarix IIV4 comparator, the clinical endpoint study in adults 18-64 years supporting licensure of the trivalent formulation demonstrated an absolute VE of 66.9% (95% CI 51.9, 77.4) against antigenically-matched culture-confirmed influenza (all cases were A/H3N2). Post-hoc sub-analyses revealed a VE of 73.4% (95% CI 59.3, 82.8) in adults 18-49 years and a VE of 13.8% (95% CI -137.0, 66.3) in adults 50-64 years. These data allow us to conclude that Fluarix is efficacious when the vaccine strain is antigenically similar to circulating influenza A/H3N2, particularly in young adults. While the Fluarix trial data raise concerns about its effectiveness as a comparator in older adults, because the trial lacked statistical power to evaluate efficacy in the age subgroups, the clinical significance of the subgroup analyses is not known.

Table 34 summarizes cases of laboratory-confirmed ILI according to influenza type and test method.

Table 34: Nasopharyngeal Swab Results for Subjects with Protocol-Defined ILI, PSC12 (Efficacy Population)

Influenza type/ Subtype or Lineage	Test Method	RIV4 # subjects with positive test	IIV4 # subjects with positive test	Total
Influenza A	rt-PCR	73	114	187
Influenza A/H3N2	rt-PCR	71	112	183
Influenza A/pandemic H1N1	rt-PCR	0	0	0
Influenza A/seasonal H1N1	rt-PCR	0	0	0
Influenza A – unable to sub-type as H3 or H1	rt-PCR	2	2	4
Influenza A	MDCK cell culture	52	93	145
Influenza B*	rt-PCR	23	24	47
Influenza B	MDCK cell culture	6	8	14
Influenza A/H3N2	Positive rt-PCR AND negative culture	21	21	42
Influenza A/H3N2	Negative rt-PCR AND positive culture	0	0	0

Source: Adapted from STN 125285/194.6, Response to 19 Feb 2016 Information Request and evaluation of the electronic datasets.
*The sponsor states that (b) (4) rt-PCR did not determine B virus lineage.

Reviewer comment: All cases of influenza A were subtype A/H3N2. The sponsor did not pursue further identification of influenza B isolates according to lineage. rt-PCR was more sensitive than cell-culture in identifying positive cases of influenza (234 vs 159 confirmed cases, respectively).

6.2.11.2 Analyses of Secondary Endpoints

Secondary Efficacy Endpoints

Table 35 presents the results of secondary analyses of rVE determined for rt-PCR-confirmed CDC-defined ILI against all influenza strains, post-hoc analyses of culture-confirmed ILI against all strains, and post hoc analyses according to influenza virus types A and B. Pre-specified secondary analyses according to antigenic similarity (matched strains) were not performed due to a laboratory error.

Table 35: Secondary and Post Hoc Analyses of Relative VE for Flublok (RIV4) versus IIV4 – PSC12 (Efficacy Population)

Analysis	RIV4 N=4303	RIV4 N=4303	IIV4 N=4301	IIV4 N=4301	RR	rVE (95% CI)
--	n (#of cases)	AR	n (# of cases)	AR	AR_{RIV4}/AR_{IIV4}	(1 - RR) x 100
Culture-confirmed protocol-defined ILI[1]	58	1.3	101	2.3	0.57	43% (21%,59%)
rt-PCR-confirmed CDC-defined ILI[2]	54	1.3	83	1.9	0.65	35% (8%,54%)
Culture-confirmed CDC-defined ILI[1]	38	0.9	64	1.5	0.59	41% (11%,61%)
rt-PCR-confirmed protocol-defined Influenza A[1]	73	1.7	114	2.7	0.64	36% (14%,53%)
rt-PCR-confirmed protocol-defined Influenza B[1]	23	0.5	24	0.6	0.96	4% (-72%,46%)

Source: STN 125285/194.9, Module 5, PSC12 CSR, Tables 14.2.2.1.1, 14.2.2.2.1, and 14.2.2.3.1 (03Mar2016).
Abbreviations: RIV4=Flublok Quadrivalent; IIV4=Fluarix Quadrivalent.
Attack Rate (AR) = # of cases of ILI / # subjects in the treatment group
Relative Risk (RR) = AR Flublok RIV4 / AR IIV4
Relative Vaccine Efficacy (rVE) of Flublok RIV4 versus IIV4 = (1 – RR) x 100
[1]Post-hoc analysis of all strains regardless of antigenic similarity
[2]Pre-specified secondary analysis of all strains regardless of antigenic similarity

Secondary and post-hoc analyses based on culture-confirmed protocol-defined ILI met criteria for non-inferior rVE as did rt-PCR and culture-confirmed CDC-defined ILI. The more stringent CDC definition requiring a fever ≥100°F in addition to cough and/or sore throat resulted in fewer cases in the analyses and wider 95% CIs as compared to the analyses based on the protocol-defined ILI. Post hoc analyses according to influenza type demonstrated non-inferior rVE for Flublok RIV4 against influenza A but failed to demonstrate non-inferior rVE against influenza B where the number of cases were fewer and 95% CIs wider (point estimate for rVE 4% with a LB of the 95% CI of –72%).

Reviewer comment: Interestingly, post hoc analyses of rVE according to influenza type A or B demonstrated lower rVE for type B strains where the antigenic similarity of circulating virus was close to vaccine strains according to CDC surveillance data. We presume that the vaccine antigens were well-matched to the B isolates but cannot be certain because the sponsor was unable to provide data regarding antigenic similarity.

Immunogenicity Endpoints

Table 36 presents the results of Day 28 post-vaccination SCRs and SCR differences between IIV4 and Flublok RIV4 for each vaccine antigen in the immunogenicity subset of the study population.

Table 36: Day 28 Post-vaccination HI SCRs and SCR differences between Flublok Quadrivalent (RIV4) and IIV4 in Adults ≥50 Years – PSC12 (Immunogenicity Population)

Strain	RIV4 SCR N=314	IIV4 SCR N=300	SCR Difference (95% CI)	Met Success Criteria?*
A/H1N1	44.9	49.0	4.1 (-3.8,12.0)	No

Strain	RIV4 SCR N=314	IIV4 SCR N=300	SCR Difference (95% CI)	Met Success Criteria?*
A/H3N2	54.5	43.3	-11.2 (-19.0,-3.3)	Yes
B /Yamagata	38.9	38.3	-0.6 (-8.2,7.2)	Yes
B/Victoria	21.0	34.3	13.3 (6.3,20.3)	No

Source: STN 125285/194.9, Module 5, PSC12 CSR, Table 14.2.4 (07Mar2016).
Abbreviations: RIV4=Flublok Quadrivalent; IIV4=Fluarix Quadrivalent; SCR=seroconversion rate.
*Success criteria for the SCR difference (SCR_{IIV4} - SCR_{RIV4}): the UB of the 95% CI must be ≤ 10%.

Table 37 presents the results of baseline and Day 28 post-vaccination GMTs and GMT ratios for IIV4 and Flublok RIV4 in the immunogenicity subset.

Table 37: HI Geometric Mean Titers (GMT) and GMT ratios of Flublok Quadrivalent (RIV4) Relative to IIV4 at Baseline and 28 Days Post-vaccination in Adults ≥50 Years – PSC12 (Immunogenicity Population)

Strain	Day	RIV4 GMT N=314	IIV4 GMT N=300	GMT Ratio (95% CI)	Met Success Criteria?*
A/H1N1	0	44 (38,51)	48 (41,56)	--	--
A/H1N1	28	190 (164,221)	220 (193,250)	1.15 (0.95,1.41)	Yes
A/H3N2	0	87 (73,103)	98 (83,117)	--	--
A/H3N2	28	522 (462,589)	358 (318,404)	0.69 (0.58,0.81)	Yes
B/Yamagata	0	17 (15,20)	18 (16,21)	--	--
B /Yamagata	28	55 (48,64)	57 (51,65)	1.03 (0.86,1.24)	Yes
B/Victoria	0	14 (12,15)	14 (13,16)	--	--
B/Victoria	28	29 (26,33)	43 (38,49)	1.47 (1.23,1.76)	No

Source: STN 125285/194.9, Module 5, PSC12 CSR, Table 14.2.3.1 (07Mar2016).
Abbreviations: RIV4=Flublok Quadrivalent; IIV4=Fluarix Quadrivalent; HI=hemagglutination inhibition; GMT=geometric mean titer.
*Success criteria for the GMT ratio (GMT_{IIV4} / GMT_{RIV4}): the UB of the 95% CI must be ≤ 1.5

Flublok RIV4 met success criteria for both non-inferior SCR differences and GMT ratios for the influenza A/H3N2 and B/Yamagata vaccine antigens but failed to meet criteria for the SCR difference for A/H1N1 and for both the SCR difference and GMT ratio for B/Victoria.

Reviewer comment: The Applicant did not have a definitive explanation for the lower immune responses elicited by Flublok RIV4 to B/Victoria as compared to IIV4, and stated that they were further evaluating the HI assay and antigens used in the assay. At the time this review was finalized, PSC had provided no additional data to shed light on this issue. Immune responses to both B antigens were low in both treatment groups at baseline and at Day 28 post-vaccination, suggesting that the low immunogenicity was due in part to a relatively immunologically naïve population. However, while it is not unusual to observe low immune responses to influenza B virus antigens, Flublok RIV4 was clearly

less immunogenic against B/Victoria as compared to IIV4 for reasons that are uncertain. Please see the related discussion in Section 6.1.11.1, PSC16, Analysis of Primary Endpoint, of this review and the DVP review for further comment. Conclusions related to the immunogenicity subset were also limited because subjects were not selected randomly and the analyses were not powered for hypothesis testing.

6.2.11.3 Subpopulation Analyses

Age Group Subanalyses

Subanalyses of rVE for rt-PCR confirmed protocol-defined ILI according to four different age groups 50-64, ≥65, 65-74, and ≥75 years yielded point estimates of rVE of 41%, 17%, 9%, and 37%, respectively, with LBs of the 95% CIs of 15%, -20%, -45%, and -25%, respectively. Subanalyses of rVE for culture-confirmed protocol-defined ILI according to four different age groups 50-64, ≥65, 65-74, and ≥75 years yielded point estimates of rVE of 42%, 43%, 30%, and 64%, respectively, with LBs of the 95% CIs of 10%, 9%, -17%, and 11%, respectively.

Upper bounds of the 95% CIs for SCR differences among the age subgroups 50-64, ≥65, 65-74, and ≥75 years were as follows:

- A/H1N1: 8.2, 23.0, 24.6, 39.6, respectively.
- A/H3N2: -2.0, -2.8, -5.6, 24.6, respectively.
- B/Yamagata: 10.3, 6.5, 6.2, 24.6, respectively.
- B/Victoria: 26.1, 11.5, 14.3, 15.8, respectively.

Upper bounds of the 95% CIs for GMT ratios among the age subgroups 50-64, ≥65, 65-74, and ≥75 years were as follows:

- A/H1N1: 1.25, 1.76, 1.79, 2.65, respectively.
- A/H3N2: 0.76, 1.09, 1.12, 1.60, respectively.
- B/Yamagata: 1.21, 1.46, 1.56, 1.79, respectively.
- B/Victoria: 1.92, 1.63, 1.88, 1.55, respectively.

Reviewer comment: rVE estimates for rt-PCR-confirmed ILI in the older age groups were lower than for adults 50-64 years of age and, while subanalyses lacked statistical power, the trend suggested that Flublok RIV4 was not non-inferior to IIV4 in adults ≥65 years. Additionally, the age group 50-64 years comprised 59.7% (2571 / 4303) of the EP and drove results of the primary endpoint analysis relative to other age subgroups. The explanation for a higher rVE in Flublok recipients ≥75 years as compared to 65-74 years is not clear. These subgroups represented 12% and 28%, respectively, of the EP, and 95% CIs were wide and overlapping (data not shown). As compared to adults 50-64 years, SCRs were lower (data not shown) and SCR differences did not meet success criteria for NI for A/H1N1 in adults ≥65 years, or for A/H1N1, A/H3N2 or B/Yamagata in adults ≥75 years of age. GMTs were lower (data not shown) and GMT ratios did not meet success criteria for NI for A/H1N1 in adults ≥65 years, or for A/H1N1, A/H3N2 or B/Yamagata in adults ≥75 years of age. No clear trends were noted for B/Victoria (NI was not demonstrated for B/Victoria in any age subgroup). Adults 50-64 years of age comprised 66.0% (405 / 614) of the immunogenicity population and drove results of the immunogenicity endpoints. Trends revealed by the age group subanalyses raise some concerns for the efficacy of Flublok RIV4 in the elderly

subpopulation ≥65 years of age. However, these analyses were not powered for hypothesis testing and must be interpreted with caution.

Sex
Subanalyses of the primary endpoint analysis of rVE according to male or female sex revealed point estimates of 33% and 31% with LBs of the 95% CIs of -4% and 1%, respectively.

UBs of the 95% CIs for SCR differences for each vaccine antigen in males versus females were as follows:

- A/H1N1: 15.9 and 14.7, respectively.
- A/H3N2: 2.6 and -1.9, respectively.
- B/Yamagata: 13.5 and 8.0, respectively.
- B/Victoria: 25.0 and 21.9, respectively.

UBs of the 95% CIs for GMT ratios for each vaccine antigen in males versus females were as follows:

- A/H1N1: 1.34 and 1.68, respectively.
- A/H3N2: 0.77 and 0.96, respectively.
- B/Yamagata: 1.41and 1.29, respectively.
- B/Victoria: 1.86 and 1.93, respectively.

Reviewer comment: rVE, SCR differences, and GMT ratios were generally similar between the male and female subpopulations.

Race and Ethnicity
Subanalyses of rVE according to racial and ethnic subgroups revealed a trend towards non-inferior rVE among blacks and African Americans [rVE = 0.64 (95% CI -0.29, 0.92)]. Similar to the overall immunogenicity subset, SCR differences and GMT ratios among blacks and African Americans showed a trend towards non-inferior immune responses to some Flublok RIV4 antigens but not others. Point estimates and UBs of the 95% CIs for SCR differences in this group were: A/H1N1 -2.6% (13.2%); A/H3N2 -16.8% (-1.3%); B/Yamagata 0.8% (16.2%); B/Victoria 16.8% (31.1%). Point estimates and UBs of the 95% CIs for GMT ratios in this group were: A/H1N1 1.07 (1.49); A/H3N2 0.76 (1.04); B/Yamagata 0.87 (1.25); B/Victoria 1.33 (1.87). The study population was not sufficiently diverse to allow meaningful subanalyses of other racial groups or persons of Hispanic/Latino ethnicity.

6.2.11.4 Dropouts and/or Discontinuations

Among the total Randomized Population, 5.5% and 5.6% of subjects in the Flublok RIV4 and IIV4 groups, respectively, withdrew early (see Section 6.2.10.1.3, Subject Disposition). The relatively low and balanced discontinuation rate was not likely to have significantly influenced interpretation of the study results. Missing data was not imputed in the prespecified efficacy, immunogenicity or safety analyses. Sensitivity analyses were performed only for subjects with missing reactogenicity data (see Section 6.2.12.2).

6.2.11.5 Exploratory and Post Hoc Analyses

Superior Vaccine Efficacy
The study protocol stated that if the primary endpoint of non-inferior VE was demonstrated, relative VE would be tested for superiority as an exploratory analysis.

Superior VE of Flublok relative to IIV4 was pre-specified as a LB of the two-sided 95% CI of rVE > 9%. Because the LB of the 95% CI for rVE was 10%, the sponsor concluded that Flublok RIV4 met prespecified criteria for superior vaccine efficacy against rt-PCR-confirmed protocol-defined ILI relative to IIV4.

Reviewer comment: Flublok RIV4 was non-inferior to IIV4 and also met protocol-specified exploratory criteria for superiority during a season of antigenic mismatch and low vaccine effectiveness for all influenza vaccines as estimated by the CDC. As previously noted, although specified in the study protocol, the SAP did not pre-specify an endpoint of superior vaccine efficacy, and CBER had also informed the sponsor in an Advice and Information Request regarding IND 15784 Amendment 15, dated July 1, 2014, that a superiority analysis would be considered exploratory. Additionally, the exploratory analysis for superiority was driven primarily by rVE against the H3N2 virus, reflecting to a lesser degree the relative performance of Flublok RIV4 against influenza B which is less certain as previously discussed. These data and the sponsor's claims of superiority for Flublok RIV4 over IIV4 will not be included in the package insert.

Effect of Influenza Vaccination in the Previous Season

Exploratory analyses of rVE according to receipt of influenza vaccine in the previous influenza season suggested a trend towards lower rVE in subjects who received vaccine in the prior season as compared to those who did not: 21% (95% CI -8%, 42%) versus 48% (95% CI 16%, 68%), respectively. Both study vaccine groups also showed a trend towards higher SCRs and post-vaccination GMTs in subjects who had not received influenza vaccine in the previous season (data not shown, see PSC12 CSR Tables 14.2.3.1 and 14.2.4). Similar trends have been reported in other recent studies, the significance of which is uncertain. This issue is the subject of ongoing influenza research. [28,51,60,61,65,66,67,73,80]

6.2.12 Safety Analyses

6.2.12.1 Methods

The Reactogenicity Population (RP) included all subjects who received known study vaccine and provided data on at least one day of the 7-day Memory Aid A for a given category of reactogenicity event. The RP was sub-divided into three categories for injection site, systemic, and febrile reactions, and was used for the analyses of pre-specified solicited AEs as described in Section 6.2.10.1. Solicited AEs were actively collected via a memory aid for seven days post-vaccination.

The Safety Population (SP) included all subjects who received a dose of study vaccine and for whom any evaluable safety data were available after vaccination, and was used for the analyses of unsolicited AEs, SAEs, and MAEs. Spontaneous, unsolicited, treatment-emergent AEs were passively collected for twenty-eight days post-vaccination. SAEs and MAEs were passively collected through the entire study period until the EOIS (minimum of six months post-vaccination). Surveillance for ILIs employed both active and passive methods. Please see Section 6.2.7 for details of safety and ILI monitoring.

6.2.12.2 Overview of Adverse Events

Among a total of 9003 subjects who were randomized, 8988 received one dose of study vaccine, and 8672 were included in the Safety Population. Twenty-five subjects from

Site 44 were vaccinated but excluded from the SP because the identity of actual treatment received could not be verified (see Section 6.2.10.1.3). A total of 8639 subjects provided local and systemic solicited AE data for Reactogenicity Populations A and B, respectively, and 8544 subjects provided solicited body temperature data for Reactogenicity Population C.

Tables 38 and 39 present an overview of solicited and unsolicited treatment-emergent adverse events (TEAEs), respectively, according to study vaccine.

Table 38: Overview of Solicited Adverse Events – PSC12 (Reactogenicity Population)

Category	RIV4 N=4312 n(%)	IIV4 N=4327 n(%)
Any solicited AE	2071 (48.0)	2206 (51.0)
• Grade 3	58 (1.3)	55 (1.3)
• Grade 4	4 (0.1)	8 (0.2)
Any solicited injection site reaction[1]	1621 (37.6)	1745 (40.4)
• Grade 3	13 (0.3)	13 (0.3)
• Grade 4	1 (0.0)	2 (0.0)
Any solicited systemic AE[2]	1077 (25.0)	1106 (25.6)
• Grade 3	42 (1.0)	44 (1.0)
• Grade 4	3 (0.1)	6 (0.1)
Any solicited febrile reaction[3]	19 (0.4)	21 (0.5)
• Grade 3	7 (0.2)	6 (0.1)
• Grade 4	0	0

Source: STN 125285/194, Module 5, PSC12 CSR, Tables 14.3.2.7.1.1.
Abbreviations: RIV4=Flublok Quadrivalent; IIV4=Fluarix Quadrivalent; AE=adverse event.
[1]Denominators for solicited injection site reactions (Reactogenicity Population A): RIV4 n=4307; IIV4 n=4319.
[2]Denominators for solicited systemic AEs (Reactogenicity Population B): RIV4 n=4306; IIV4 n=4318.
[3]Denominators for febrile reactions (Reactogenicity Population C): RIV4 n=4262; IIV4 n=4282.

Table 39: Overview of Unsolicited Treatment-Emergent Adverse Events – PSC12 (Safety Population)

Category	RIV4 N=4328 n(%)	IIV4 N=4344 n(%)
Any unsolicited TEAE*	601 (13.9)	614 (14.1)
-Grade 1 (mild)	345 (8.0)	350 (8.1)
-Grade 2 (moderate)	213 (4.9)	220 (5.1)
-Grade 3 (severe)	43 (1.0)	43 (1.0)
-Grade 4 (life-threatening)	0	0
• Treatment-related unsolicited TEAEs*	61 (1.4)	72 (1.7)
TEAEs leading to discontinuation (excluding deaths)**	2 (0.0)	0 (0.0)
Serious TEAEs (SAEs)**	146 (3.4)	133 (3.1)
• Treatment-related serious TEAEs (SAEs)**	0	1 (0.0)
Deaths**	8 (0.2)	12 (0.3)
Any MAE**	775 (17.9)	786 (18.1)
• Treatment-related MAEs**	21 (0.5)	21 (0.5)

Source: STN 125285/194, Module 5, PSC12 CSR, Table 14.3.2.1.1; STN 125285/194.2, Tables 14.3.2.1.1.a and 14.3.2.3.1.a; and STN 125285/194.3, Table 4-1.
Abbreviations: RIV4=Flublok Quadrivalent; IIV4=Fluarix Quadrivalent; TEAE=treatment-emergent adverse event; SAE=serious adverse event; MAE=medically-attended adverse event.
*Through Day 28
**Through Day 180

In a response to our January 11, 2016 request for information (STN 125285/194.3), PSC clarified several discrepancies in the report of discontinuations due to AEs. In addition to twenty deaths (Flublok n=8; IIV4 n=12), two Flublok RIV4 recipients were discontinued due to AEs and are described in Section 6.2.12.7.

Solicited Adverse Events

Solicited Local Adverse Events

Table 40 summarizes the rates of solicited local AEs reported in the seven days following vaccination (Day 0 through Day 7) in subjects ≥50 years of age according to treatment group, overall and by maximum severity grade.

Table 40: Solicited Local Injection Site Reactions, Overall, Grades 3 and 4, Subjects Aged ≥50 Years, Day 0 through Day 7 Post-Vaccination – PSC12 (Reactogenicity Population)

Treatment	RIV4 N=4312	RIV4 N=4312	RIV4 N=4312	IIV4 N=4327	IIV4 N=4327	IIV4 N=4327
Severity Grade	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Local Solicited AE	n(%)[1]	n(%)[2]	n(%)[2]	n(%)[1]	n(%)[2]	n(%)[2]
Any Local AE[1]	1621 (37.6)	13 (0.3)	1 (0.0)	1745 (40.4)	13 (0.3)	2 (0.0)
Local pain[2]	813 (18.9)	5 (0.1)	0	950 (22.0)	8 (0.2)	1 (0.0)
Local tenderness[2]	1479 (34.3)	6 (0.1)	1 (0.0)	1604 (37.1)	10 (0.2)	2 (0.0)
Local redness[2]	122 (2.8)	2 (0.0)	0	87 (2.0)	1 (0.0)	0
Local firmness/swelling[2]	142 (3.3)	1 (0.0)	0	115 (2.7)	2 (0.0)	0

Source: STN 125285/194, Module 5, PSC12 CSR, Table 14.3.2.7.1.1.
Abbreviations: RIV4=Flublok Quadrivalent, IIV4=Fluarix Quadrivalent; AE=adverse event.
[1]n represents the number of subjects in each treatment group who experienced symptoms even if severity grades were missing; denominator for percentage is number of subjects in the Reactogenicity Population A for the treatment group: RIV4 n=4307; IIV4 n=4319.
[2]Denominator for the percentage excludes subjects in each treatment group who were missing severity data for all 7 days of the solicited AE period: for RIV4, n=4307; for IIV4 n=4319 (for all parameters).

The most common local reactogenicity events following study vaccinations were injection site tenderness (RIV4 34.3%, IIV4 37.1%) and pain (RIV4 18.9%, IIV4 22.0%), mostly Grade 1 to Grade 2 (mild to moderate) in severity. Rates and severity of local injection site reactions were similar between treatment groups. Grade 3 and 4 reactions were rare (0%-0.3%).

Local reactions began between Days 0 and 1 in the majority of subjects and had a mean duration 2.0 to 2.1 days, similar between treatment groups.

Reviewer comment: No imbalance in the frequencies of local redness (2.8% vs 2.0%, respectively) among adults ≥50 years was observed between Flublok RIV4 and IIV4 groups, in contrast to adults 18-49 years (PSC16) where local redness which occurred more frequently in the Flublok RIV4 group as compared to IIV4 (4.2% vs 0.9%).

Solicited Systemic Adverse Events Including Fever

Table 41 summarizes the rates of solicited systemic AEs reported in the seven days following vaccination (Day 0 through Day 7) in subjects ≥50 years of age according to treatment group, overall and by maximum severity grade.

Table 41: Solicited Systemic Adverse Events and Fever, Overall, Grades 3 and 4, Subjects Aged ≥50 Years, Day 0 through Day 7 Post-Vaccination – PSC12 (Reactogenicity Population)

Treatment	RIV4 N=4312	RIV4 N=4312	RIV4 N=4312	IIV4 N=4327	IIV4 N=4327	IIV4 N=4327
Severity Grade	**Any**	**Grade 3**	**Grade 4**	**Any**	**Grade 3**	**Grade 4**
Systemic Solicited AE	**n(%)[1]**	**n(%)[2]**	**n(%)[2]**	**n(%)[1]**	**n(%)[2]**	**n(%)[2]**
Any Systemic AE[1]	1077 (25.0)	42 (1.0)	3 (0.1)	1106 (25.6)	44 (1.0)	6 (0.1)
Fatigue[2]	526 (12.2)	19 (0.4)	0	521 (12.1)	15 (0.3)	6 (0.1)
Shivering/chills[2]	204 (4.7)	10 (0.2)	0	187 (4.3)	15 (0.3)	2 (0.0)
Joint pain[2]	324 (7.5)	9 (0.2)	0	346 (8.0)	18 (0.4)	2 (0.0)
Muscle pain[2]	366 (8.5)	12 (0.3)	2 (0.0)	378 (8.8)	13 (0.3)	1 (0.0)
Headache[2]	549 (12.7)	11 (0.3)	1 (0.0)	582 (13.5)	21 (0.5)	2 (0.0)
Nausea[2]	212 (4.9)	7 (0.2)	0	213 (4.9)	9 (0.2)	1 (0.0)
Fever[3]	19 (0.4)	7 (0.2)	0	21 (0.5)	6 (0.1)	0

Source: STN 125285/194, Module 5, PSC12 CSR, Table 14.3.2.7.1.1.
Abbreviations: RIV4=Flublok Quadrivalent, IIV4=Fluarix Quadrivalent; AE=adverse event.
[1]n represents the number of subjects in each treatment group who experienced symptoms even if severity grades were missing; denominator for percentage is number of subjects in the Reactogenicity Population B for the treatment group: RIV4 n=4306; IIV4 n=4318.
[2]Denominator for the percentage excludes subjects in each treatment group who were missing severity data for all 7 days of the solicited AE period: for RIV4, n=4306; for IIV4 n=4318 (for all parameters).
[3]Denominator for the percentage excludes subjects in each treatment group who were missing severity data for all 7 days of the solicited AE period for fever: RIV4 n=4262; IIV4 n=4282. Grade 1=100.4°F-101.1°F; Grade 2=101.2°F-102.0°F; Grade 3=102.1°F-104°F; Grade 4>104°F.

Approximately 25% of the study population experienced at least one solicited systemic AE. Individual events occurred at similar rates between treatment groups. The most commonly reported symptoms were headache (RIV4 12.7%, IIV4 13.5%), fatigue (RIV4 12.2%, IIV4 12.2%), muscle pain (RIV4 8.5%, IIV4 8.8%), and joint pain (RIV4 7.5%, IIV4 8.0%). Most events were mild to moderate (Grade 1 or Grade 2) in severity. Rates of Grade 3 and Grade 4 events were ≤0.4% and 0.0-0.1%, respectively. Most solicited systemic symptoms began between Day 1 and Day 2, and persisted for a mean duration of 1.9 to 2.0 days.

Sensitivity analyses were performed by imputing a Grade 3 (severe) for subjects with missing reactogenicity data, and did not change the overall interpretation of either the solicited local or systemic AE results (data not shown, see PSC12 CSR Table 14.3.2.7.6.1).

Reviewer comment: Rates, severity, and duration of local and systemic reactogenicity events were consistent with previous clinical trial data for Flublok (trivalent formulation), were not unusual for the comparator IIV4, and were similar between treatment groups.

Subpopulation Analyses of Solicited Adverse Events

In both treatment groups, local injection site reactions (primarily pain and/or tenderness) were reported more frequently among females, whites, non-Hispanics, and younger subjects (50-64 years of age) as compared to males, non-whites, Hispanics, and older adults (≥65 years of age) [rates of any solicited local reaction 45.4%, 39.9%, 38.2%, and 53.0% versus 26.7%, 28.5%, 27.3%, and 40.8%, respectively. See PSC12 CSR Tables 14.3.2.7.2.1, 14.3.2.7.3.1, 14.3.2.7.4.1, and 14.3.7.2.5.1 for individual event rates]. Females reported slightly more systemic symptoms overall as compared to males (27.3% versus 21.8%), with the largest difference observed in the frequency of

headache (14.6% vs 10.1%). All systemic symptoms were reported more frequently by younger adults as compared to adults ≥65 years of age (rates of ≥1 systemic symptom 29.0% vs 19.2%). Only small differences were observed in the rates of solicited systemic symptoms between whites and non-whites (rates of ≥1 systemic symptom 24.6% vs 26.6%, respectively) and between non-Hispanics and Hispanics (25.2% vs 20.5%).

Reviewer comment: Trend towards higher rates of solicited local and systemic AEs in females and younger adults as compared to males and elderly adults have been observed in other influenza vaccine studies. The numbers of subjects belonging to racial groups other than whites or blacks or of Hispanic ethnicity were too small for meaningful comparisons of the rates of solicited adverse events in these subpopulations.

Unsolicited Adverse Events (Day 0 through Day 28)
Unsolicited treatment-emergent AEs (TEAEs) were collected from immediately after vaccination through Day 28 and categorized according to MedDRA preferred term (PT) and system organ class (SOC). Subjects were counted once per PT and per SOC, once per maximum intensity for each category, and once by closest relationship to study vaccine. Although safety laboratories were not collected systematically, some laboratory abnormalities obtained in the evaluation of AEs were reported as unsolicited AEs, based on the judgment of the investigators.

A total of 1215 (14.0%) subjects reported TEAEs in the 28 days following vaccination, with similar proportions between treatment groups: Flublok RIV4 13.9% vs IIV4 14.1%. System Organ Class categories with the highest overall rates of AEs in the RIV4 and IIV4 treatment groups, respectively, were: Respiratory, Thoracic, and Mediastinal Disorders (4.5% vs 5.1%), primarily cough (2.1% vs 2.6%), oropharyngeal pain (1.9% of both groups), and productive cough (0.5% vs 1.0%); Infections and Infestations (4.0% vs 3.9%), primarily upper respiratory infection (1.0% vs 1.1%); General Disorders and Administration Site Conditions (3.2% of both groups), primarily fatigue (1.1% of both groups) and ILI (1.0% of both groups); Nervous System Disorders (2.3% vs 2.4%), primarily headache (1.7% vs 1.8%); Musculoskeletal and Connective Tissue Disorders (2.1% vs 1.8%), primarily myalgia (1.0% vs 0.7%); and Gastrointestinal Disorders (1.3% of both groups), no single event with a rate ≥1%.

Most subjects experienced unsolicited AEs assessed as mild (8.0% and 8.1% of all RIV4 and IIV4 subjects, respectively) or moderate (4.9% and 5.1% of RIV4 and IIV4 subjects, respectively) in severity. A total of 1.0% of subjects in each treatment group reported severe (Grade 3) events. No subjects experienced life threatening (Grade 4) unsolicited AEs.

Two non-fatal AEs lead to discontinuation (RIV4 n=2; IIV4 n=0) (see Section 6.2.12.7).

<u>Severe Non-Serious Unsolicited AEs</u>
Slightly more Flublok RIV4 than IIV4 recipients overall, 167 (3.9%) versus 141 (3.2%) respectively, reported severe (Grade 3) events (serious and non-serious). However, no large imbalances in specific MedDRA SOC or PT categories were identified between treatment groups. Severe non-serious unsolicited AEs were further evaluated by review of the electronic datasets. Only three cases appeared potentially related to Flublok RIV4, based on temporal relationship to vaccination, biological plausibility, or the

Applicant's assessment of relatedness, and are summarized below. Please see Sections 6.2.12.3 and 6.2.12.4 for a review of severe events also categorized as serious.

- Subject #(b) (6) was a 50 year old non-Hispanic white female, with a history of cervical cancer and diverticulosis, who received Flublok RIV4 on (b) (6), and experienced five severe non-serious AEs of headache, vomiting, epistaxis, fatigue, and a hordeolum (sty) on the day of vaccination. No specific action was taken. Epistaxis and vomiting resolved on the day of onset and the remaining symptoms resolved on Day 5. The investigator assessed the AEs as related to the study vaccine. According to the case narrative requested for this subject, the Applicant assessed the AEs as not related, and stated that they did not appear severe in intensity. No other information was available.

- Subject #(b) (6) was a 53 year old non-Hispanic black female who received Flublok RIV4 on (b) (6), and experienced a severe non-serious headache on December 4, 2014 assessed as related to study vaccine. It resolved after 18 days without specific treatment.

- Subject #(b) (6) was a 53 year old non-Hispanic white female who had onset of severe non-serious joint pain on study Day 13, assessed as related to Flublok RIV4. The AE resolved after 32 days without specific treatment.

Reviewer comment: It is difficult to assess the relatedness of the headache, vomiting, and/or joint pain experienced by these subjects. However, the events were not serious and resolved. As noted, IIV4 recipients experienced similar rates of severe unsolicited AEs, many of which were also assessed as related to study vaccine. No unusual safety concerns were raised by these data.

Subpopulation Analyses of Unsolicited Adverse Events

Females reported more AEs than males for most SOC categories (Flublok RIV4 female vs male recipients 15.4% vs 11.7%; IIV4 female vs male recipients 16.0% vs 11.5%), but rates and severity grades were similar between treatment groups (see PSC12 CSR Tables 14.3.2.2.2.1.a and 14.3.2.3.2.1.a). Individual event rate differences between females and males (categorized by PT) were small (<2%). Rates and severity of unsolicited AEs were similar both between whites and non-whites and treatment groups (Flublok RIV4 white vs non-white recipients 13.9% vs 13.7%, overall; IIV4 white vs non-white recipients 14.4% vs 13.3%, overall) (see PSC12 CSR Tables 14.3.2.2.4.1.a and 14.3.2.3.4.1.a). Blacks/African Americans comprised the majority of non-white racial groups. Rates of unsolicited AEs among Hispanics/Latinos were slightly lower as compared to non-Hispanics/Latinos in both treatment groups (Flublok RIV4 Hispanic/Latino vs non-Hispanic/Latino 10.7% vs 14.0%; IIV4 Hispanic/Latino vs non-Hispanic/Latino 11.9% vs 14.3%) but severity grades were similar. Age subset analyses did not reveal imbalances in the incidence or severity of unsolicited AEs (data not shown, see PSC12 CSR Tables 14.3.2.2.3.1.a and 14.3.2.3.3.1.a for details).

6.2.12.3 Deaths

Twenty subjects died during the six month post-vaccination study period, eight among Flublok RIV4 recipients and twelve among IIV4 recipients. Table 42 summarizes deaths by treatment group, causal adverse event, and relationship to vaccination as assessed

by the investigator and Applicant. None of the deaths were considered related to study vaccine.

Table 42: Summary of Deaths following Vaccination (Days 0 to ~180) – PSC12 (Safety Population)

Group	Subject ID	Age/ Sex	Cause of Death by Preferred Term	Onset*	Death*	Related**
RIV4	(b) (6)	67M	Found dead, cause unknown	(b) (6)	(b) (6)	No
RIV4		69F	Unspecified			No
RIV4		60F	Motor vehicle accident			No
RIV4		52F	Seizure			No
RIV4		68F	Myocardial infarction			No
RIV4		59M	Drug overdose			No
RIV4		85F	Cardiac arrest			No
RIV4		70M	Head trauma			No
IIV4		84F	Unspecified			No
IIV4		85F	Road traffic accident			No
IIV4		82M	Myocardial infarction			No
IIV4		53M	Drug overdose			No
IIV4		60M	Cardiac arrest			No
IIV4		75M	Head trauma			No
IIV4		55M	Liver cancer, primary			No
IIV4		64M	Lung cancer, metastatic			No
IIV4		55F	Liver cancer, primary or metastatic			No
IIV4		53F	Liver cancer, primary or metastatic			No
IIV4		88M	Respiratory failure (pneumonia)			No
IIV4		54M	Pulmonary embolism, cardiac arrest			No

Source: Adapted from STN 125285/194, Module 5, PSC12 CSR, Table 35, Listing 16.2.7.4, Serious Adverse Event Narratives Appendix 14.3.3, and electronic datasets.
*Number of days post-vaccination
**Investigator and Applicant's assessment of causality.

Reviewer comment: Fewer Flublok RIV4 recipients died during the six month safety follow-up period as compared to IIV4. Case narratives were reviewed and this reviewer agrees with the Applicant's assessment that deaths following vaccination with Flublok RIV4 and IIV4 were not related to the study vaccine due to lack of a close temporal relationship, a more plausible alternative etiology exists, or lack of biological plausibility.

6.2.12.4 Nonfatal Serious Adverse Events

The Applicant reports that a total of 145 (3.4%) and 132 (3.0%) subjects in the Flublok RIV4 and IIV4 treatment groups, respectively, had SAEs over the six month safety follow-up period. Of these, 25 (0.6%) and 22 (0.5%) Flublok RIV4 and IIV4 recipients, respectively, had 29 and 30 SAEs, respectively, that occurred in the 28 days post-vaccination. The most common SAEs, reported in 0.5% to 0.6% of Flublok RIV4 or IIV4 recipients, respectively, from Day 0 through Day 180, occurred in the following MedDRA SOC categories: Infections and Infestations (0.4% vs 0.6%), Cardiac Disorders (0.5% vs 0.4%), Musculoskeletal and Connective Tissue Disorders (0.5% vs 0.4%), Gastrointestinal Disorders (0.5% vs 0.2%), and Neoplasms, Benign, Malignant, and Unspecified (0.2% vs 0.5%). In the 28 days post-vaccination, SAEs, as categorized by MedDRA SOC or PT, occurred with frequencies of ≤0.1%.

Reviewer comment: The types and frequencies of SAEs from Day 0 through Day 28 and Day 180 were balanced between treatment groups. No individual event, as categorized by MedDRA PT occurred with a frequency of ≥1% and no large imbalances occurred in rates of events between treatment groups among SOC or PT categories.

Reviewer comment: Review of non-fatal SAEs, including the Applicant's case narratives, indicated that the vast majority were events that occur commonly in an older adult and elderly population. None of the SAEs appeared clearly related to the study vaccines with the possible exception of Subject (b) (6) ***who experienced atrial fibrillation and a CVA on the day following vaccination with Flublok RIV4. Although, in this reviewer's opinion, it is more likely that other risk factors for these events in this subject were causal, the close temporal relationship to vaccination and overall poor quality of the data make it difficult to exclude allergic reactions or reactogenicity as being contributory. For the other SAEs, the absence of a close temporal relationship and biological plausibility and/or presence of more plausible alternative etiologies enabled the reviewer to assess relatedness as unlikely despite the overall poor quality of the Applicant's data.***

Subpopulation Analyses of Serious Adverse Events (Fatal and Non-Fatal)
Subanalyses according to sex, race, and ethnicity revealed higher proportions of whites/Caucasians who experienced SAEs as compared to blacks/African Americans (Flublok RIV4 2.6% vs 0.7%; IIV4 2.3% vs 0.6%, respectively) as well as in non-Hispanic/Latinos as compared to Hispanic/Latinos (Flublok RIV4 3.2% vs 0.1% vs IIV4 2.8% vs 0.3%, respectively). No large differences in the overall rate of SAEs between sexes or in the rates of death among any of the subpopulations were observed.

Reviewer comment: The Applicant reported that "tabulations of safety events for the demographic subsets of gender, race and ethnicity revealed no significant differences with respect to SAEs or MAEs", but did not provide these analyses in the CSR until after a request for information (STN 125285/194.3). The study was not powered to draw definitive conclusions from the observed trends.

6.2.12.5 Adverse Events of Special Interest (AESI)

Medically-Attended Events (MAEs)
Similar proportions of Flublok RIV4 and IIV4 recipients experienced MAEs during the six month post-vaccination follow-up period (17.9% vs 18.1%, respectively), with no large imbalances observed among SOC categories. Subpopulation analyses in both treatment groups revealed trends towards more MAEs among females than males (Flublok RIV4 11.7% vs 6.2%; IIV4 11.9% vs 6.2%), whites/Caucasians than blacks/African Americans (Flublok RIV4 15.0% vs 2.6%; IIV4 15.5% vs 2.1%), and non-Hispanic/Latinos than Hispanic/Latinos (Flublok RIV4 17.2% vs 0.7%; IIV4 17.3% vs 0.8%). The largest imbalances were observed in the SOC categories of Infections and Infestations, Respiratory, Thoracic, and Mediastinal Disorders, and General Disorders and Administration Site Conditions, without notable imbalances for specific preferred terms, including influenza or ILI.

Reviewer comment: The imbalances in the incidence of MAES observed in subpopulation analyses are contrary to the Applicant's report that no differences

were observed (PSC12 CSR, p.78). However, the study was not powered to draw definitive conclusions from the observed trends.

The study protocol did not define AESIs as specific safety endpoints. However, the CSR and electronic datasets were evaluated for events representing potential risks that have been associated with influenza vaccines: hypersensitivity (including anaphylaxis and serum sickness), encephalomyelitis, transverse myelitis, Guillain-Barre syndrome (GBS), Bell's Palsy, optic neuritis, and seizures or convulsions. Due to a case of unexplained pleuropericarditis reported in an earlier study, PSC04, the datasets were also evaluated for cases of pleuritis, pleuropericarditis, pericarditis, and myocarditis, but none were found. Two Flublok RIV4 recipients (b) (6)) and one IIV4 recipient, #(b) (6)) experienced convulsions 14, 133, and 70 days post-vaccination, respectively, that appeared unrelated to study vaccine. Five subjects (Flublok RIV4 recipient #(b) (6) ; IIV4 recipients (b) (6)) had various neuralgias that also appeared unrelated primarily due to late onset in relation to vaccination. Subject #(b) (6) , a 79 year old white non-Latino female with a history of hypertension and total hip replacement, was diagnosed with moderate Bell's palsy 85 days after receiving Flublok RIV4 on (b) (6) . The CRF and a case narrative were requested for this subject and reviewed, and indicated that the deficit resolved completely 18 days after onset and treatment with prednisone. No other information was provided. Scientific literature estimates that the rate of Bell's Palsy following influenza vaccination is approximately 0.15-0.46 reports per million doses distributed.[93] The annual background rate is ~25 cases per 100,000 people.[78] Most cases are caused by herpes simplex virus, followed by varicella zoster and other viruses, including influenza. Evidence is insufficient to establish a causal relationship between influenza vaccination and Bell's Palsy. In the case of Subject #(b) (6) , the prolonged interval between vaccination and diagnosis also argues against a causal effect. However, the failure of the Applicant to provide details regarding the evaluation of the subject including an investigation of alternative etiologies, represents a limitation of the study data.

No other AESIs were reported in this study except for hypersensitivity type events which are discussed separately below.

<u>Hypersensitivity Type Events</u>
Collection and analyses of hypersensitivity type events were not pre-specified. The reviewer evaluated the CSR and electronic datasets post hoc for acute potential hypersensitivity type events (as described for PSC16 in Section 6.1.12.5) that occurred within 7 days of receiving the study vaccines (Day 0 through Day 6). Table 43 summarizes these events according to MedDRA preferred term and treatment group. Diarrhea was included in the summary because it may accompany an anaphylactic reaction, and because some AEs of diarrhea occurred shortly after vaccination and were assessed as related. Extending evaluation of the datasets through Day 28 yielded one additional subject, #(b) (6) , who had an unspecified mild non-serious allergy/hypersensitivity event 10 days after receiving Flublok RIV4.

In many instances, the Applicant provided insufficient information to allow an assessment of causality. However, all events were non-serious and most were mild with the exception of two cases: Flublok RIV4 recipient #(b) (6) , a 51 year old white, non-Latino female with a history of cervical cancer and several surgeries, reported severe vomiting, epistaxis, headache, fatigue, and hordeolum on the day of vaccination

with Flublok RIV4 ((b) (6)). All symptoms resolved spontaneously within five days without seeking medical care. IIV4 recipient #(b) (6) , an 84 year old white female, developed a severe drug eruption two days post-vaccination which resolved after treatment with methylprednisolone, diphenylhydramine, and topical hydrocortisone cream.

Table 43: Summary of Potential Hypersensitivity Events Occurring from Day 0 through Day 6 Post-Vaccination according to Treatment Group – PSC12 (Safety Population)*

Adverse Event (MedDRA PT)	**Flublok N=4328 N**	**IIV4 N=4344 N**
Diarrhea	5	10
Injection site vesicles	0	1
Presyncope	1	0
Asthma	1	0
Wheezing	1	0
Dermatitis	0	1
Drug eruption	0	1
Pruritus	5	4
Rash	2	2
Skin lesion	1	0
Swelling face	0	1
Urticaria	1	0
Hypersensitivity*	1	0

Source: STN 125285/194, Module 5, PSC12 CSR, Tables 14.3.2.2.1.1 and 14.3.2.3.1.1 and evaluation of the electronic datasets.
*Subject #(b) (6) experienced hypersensitivity (AE term "allergy") on Study Day 10.

Reviewer comment: AESIs and hypersensitivity type events potentially related to study vaccines reported in the 7 days following vaccination were uncommon (for each type of event ≤0.1% and collectively <0.5% per treatment group even if we assumed that they were related to the study vaccines) and generally balanced between treatment groups except for diarrhea which occurred in twice as many IIV4 than Flublok RIV4 recipients (n=10 vs n=5). The clinical significance of the small imbalance of diarrheal events favoring Flublok is uncertain, is the opposite of the small imbalance in favor of IIV4 observed in PSC16, and may have occurred by chance alone. Among Flublok recipients, one case of severe headache and vomiting, one case of presyncope, and four cases of "allergy", pruritus, hives, vomiting and/or diarrhea were possibly related to study vaccine in the opinion of the reviewer. One IIV4 recipient experienced a severe drug eruption. No cases of anaphylaxis occurred post-vaccination. Flublok was not associated with a greater risk of acute hypersensitivity in this population of adults ≥50 years of age. The lack of documentation for some of the events, i.e., more detailed descriptions and evaluations by study staff or external healthcare providers, limits our ability to assess causality and represents a limitation of the safety data.

6.2.12.6 Clinical Test Results

Clinical safety laboratories were not collected systematically in this study.

6.2.12.7 Dropouts and/or Discontinuations

As noted in Sections 6.2.10.1.3 and 6.2.11.4, because early withdrawal rates (Flublok RIV4 5.5%, IIV4 5.6%) were relatively low and balanced between treatment groups, discontinuations were unlikely to have significantly influenced the evaluation of safety.

In addition to the twenty subjects who died during the study (Flublok RIV4 n=8; IIV4 n=12), two other subjects discontinued due to AEs. Subject #(b) (6), a 70 year old non-Hispanic white male with a history of hearing loss and osteoporosis but no prior psychiatric diagnosis, received Flublok RIV4 on (b) (6) and experienced an AE of "adjustment disorder" on November 14, 2015, 14 days post-vaccination. The AE was assessed as non-serious, moderate in severity, unrelated to study vaccine, and ongoing when the subject was withdrawn from the study on Day 17. The Applicant's narrative and CRF provided no other details.

The second discontinuation due to an AE was Flublok RIV4 recipient Subject #(b) (6), a 55 year old black/African American male with cardiovascular disease who was hospitalized with an intestinal perforation 20 days post-vaccination, complicated by an abdominal abscess and renal failure. He was re-admitted with an exacerbation of diverticulitis 76 days post-vaccination. The Applicant notes that the subject was subsequently lost to follow-up and did not complete the study. According to the electronic datasets and the Applicant's report, the previous SAEs did not lead to discontinuation and the precise reason for discontinuation was not known, but the reason for discontinuation was categorized as being due to an AE.

Reviewer comment: These AEs appear unrelated to study vaccine due to a lack of close temporal relationship and biological plausibility.

6.2.13 Study Summary and Conclusions

Efficacy and Immunogenicity Conclusions

- Flublok RIV4 met pre-specified success criteria for the primary endpoint analysis of non-inferior relative vaccine efficacy against rt-PCR-confirmed, protocol-defined ILI (all strains regardless of antigenic similarity to vaccine antigens) as compared to U.S.-licensed IIV4 [rVE 30% (95% CI: 10%, 47%)].
- Flublok RIV4 also met secondary and post-hoc endpoints evaluating non-inferior relative vaccine efficacy using an alternative CDC definition of ILI and when confirmation of ILI was based on cell culture using either protocol- or CDC-defined ILI.
- The majority of cases of influenza were due to influenza A/H3N2 most of which were probably antigenically distinct from the vaccine A/H3N2 strains based on CDC and global surveillance studies for the 2014-2015 influenza season. The Applicant was unable to perform antigenic or phylogenetic characterization of study isolates which may have enhanced our understanding of the degree to which study isolates differed from vaccine antigens.
- Relative VE against influenza B viruses [rVE 4% (95% CI: -72%, 46%)], which were antigenically well-matched to 2014-2015 vaccine strains according to CDC surveillance data, was lower than the rVE against influenza A/H3N2.
- Flublok RIV4 did not elicit consistent non-inferior immune responses relative to IIV4. Flublok met success criteria for non-inferior SCR differences and GMT ratios for the A/H3N1 and B/Yamagata vaccine antigens, but failed to meet these criteria for the SCR difference for A/H1N1 and failed both the SCR difference and

GMT ratio for B/Victoria. Explanations for the low immune responses to Flublok's B antigens may include a population immunologically naïve to B/Brisbane/60/2008, the use of whole virus and/or egg-derived antigens in the HI assay, or other unidentified issues. Interference from the second B antigen and suboptimal potency were unlikely according to the DVP reviewer. The Applicant attributed the low immunogenicity of the B virus strains to the use of egg-derived antigens in the HI assay and supported this claim by stating that the clinical efficacy of Flublok and IIV4 against influenza B were comparable. However, the 95% CI for the rVE of 4% against influenza B was wide with a very low LB (95% CI: -72%, 46%) and, despite being antigenically well-matched to wild type B viruses, the rVE of Flublok RIV4 against the B strains was lower as compared to A/H3N2. In this reviewer's opinion, the rVE results for Flublok against influenza B are inconclusive and do not provide reassurance or allow us to disregard the immunogenicity results for the B strains. Assuming that other potential explanations are excluded, repeat serologies in a subset of subjects using BEVS-derived antigens in the HI assay might have been informative in exploring the Applicant's theory that the lower immunogenicity of Flublok RIV4 against B viruses is due to a disadvantage related to the use of egg-derived antigens in the HI assay. However, such a study would not have provided conclusive evidence to support PSC's theory. Finally, we must keep in mind that the immunogenicity analyses were descriptive and limited by a lack of randomization.

- Analyses according to age subgroups showed a trend towards lower rVE for Flublok RIV4 in adults ≥65 years as compared to adults 50-64 years, and, although subgroup analyses lacked statistical power, Flublok in these older age groups did not meet criteria for non-inferior rVE. As compared to adults 50-64 years, a trend towards lower SCRs and GMTs and higher SCR differences and GMT ratios (i.e., not non-inferior to IIV4) was observed in adults ≥65 years for A/H1N1 and in adults ≥75 years for A/H1N1, A/H3N2, and B/Yamagata. Age group subanalyses of non-inferior immune responses to B/Victoria showed no clear trends (NI criteria were not met in any age subgroup). Adults 50-64 years comprised 59.7% of the Efficacy Population and 66.0% of the Immunogenicity Population, driving results of the primary rVE analysis and immunogenicity endpoints, respectively.
- Subanalyses of efficacy and immunogenicity according to sex, race, and ethnicity demonstrated trends similar to the overall study population.
- Flublok RIV4 met pre-specified success criteria for non-inferior rVE and exploratory criteria for superiority relative to IIV4 in a season of antigenic mismatch for the predominant A/H3N2 strain where overall vaccine efficacy was very low. These endpoints were more difficult to meet than if A/H3N2 vaccine antigen had been well-matched to circulating strains. Overall, these data support traditional approval of Flublok RIV4 in adults ≥18 years. However, uncertainties and limitations of the data include the following:
    - The validity of a non-inferiority study depends on the effectiveness of the comparator. For PSC12, the effectiveness of the IIV4 comparator was uncertain due to two factors: 1) CDC data indicates that vaccine effectiveness was exceptionally low for all flu vaccines during the 2014-2015 study period, and 2) the study supporting licensure of Fluarix (trivalent formulation) showed an absolute VE of only 13.8% (LB 95% CI: -137%) in a subanalysis of adults 50-64 years. [59,74]

- Secondary immunogenicity endpoint results were inconsistent, particularly for the B strain but also for A/H1N1, against which Flublok RIV4 elicited lower immune responses relative to IIV4.
- Trends revealed by age group subanalyses suggest lower rVE and immunogenicity in subjects ≥65 years.
- The rVE results in adults ≥50 years may not be generalizable to other comparator vaccines, seasons with better antigenic matching between comparator vaccines and wildtype virus, or to seasons where B strains are more prevalent. These uncertainties are of particular concern in the elderly subpopulation ≥65 years of age that is at greater risk for serious complications of influenza.
- The Applicant did not perform antigenic or genetic characterization of isolates. We reasonably assume the majority of A/H3N2 viruses were antigenically mismatched based on CDC and global surveillance data.

Safety Conclusions

Overall, the safety of Flublok RIV4 was acceptable and comparable to IIV4 in adults ≥50 years of age. The rates and severity of solicited local injection site reactions (primarily tenderness and pain) and systemic symptoms (primarily headache, fatigue, muscle pain and joint pain) in the seven days following vaccination with Flublok RIV4 and IIV4 were similar between treatment groups. Most events were mild to moderate in severity and short in duration. Subpopulation analyses of solicited AEs demonstrated more frequent local injection site pain and/or tenderness in both treatment groups among females, whites, non-Hispanics, and younger subjects (50-64 years of age) as compared to males, non-whites, Hispanics, or older adults (≥65 years of age). Females also reported slightly more systemic symptoms overall as compared to males, primarily headache (14.6% vs 10.1%). Younger adults 50-64 years of age reported all solicited systemic symptoms more frequently than adults ≥65 years of age (29.0% vs 19.2%, respectively, overall). Only small differences were observed in the rates of solicited systemic symptoms between whites and non-whites and between non-Hispanics and Hispanics. A trend towards higher rates of solicited local and systemic AEs in females and younger adults as compared to males and elderly adults has been observed in other influenza vaccine studies.

A total of 1215 (14.0%) subjects reported treatment emergent unsolicited AEs in the 28 days following vaccination, with similar proportions between treatment groups. Individual AEs were low in frequency (≤2.6%) and mostly mild to moderate in severity. No large imbalances, unusual patterns, or specific safety concerns, including hypersensitivity events, were identified. Subpopulation analyses of unsolicited AEs revealed that females reported more AEs than males for most SOC categories, however, rates and severity grades were similar between treatment groups. Rates and severity of unsolicited AEs were similar both between whites and non-whites and between treatment groups. Rates of unsolicited AEs among Hispanics/Latinos were slightly lower as compared to non-Hispanics/Latinos in both treatment groups, but severity grades were similar. Age subset analyses did not reveal imbalances in the incidence or severity of unsolicited AEs.

Twenty subjects died during the six month post-vaccination study period, eight among Flublok RIV4 recipients and twelve among IIV4 recipients. None of the deaths appeared related to study vaccine.

A total of 145 (3.4%) and 132 (3.0%) subjects in the Flublok RIV4 and IIV4 treatment groups, respectively, experienced SAEs over the six month safety follow-up period. Of these, 25 (0.6%) and 22 (0.5%) Flublok RIV4 and IIV4 recipients, respectively, had SAEs that occurred in the 28 days post-vaccination. The types and frequencies of SAEs through Day 28 and Day 180 were balanced between treatment groups. No individual event, as categorized by MedDRA PT, occurred with a frequency of ≥1%. Most SAEs were events that occur commonly in an older adult and elderly population. No SAEs appeared clearly related to study vaccines. Subanalyses according to sex, race, and ethnicity revealed higher proportions of whites/Caucasians who experienced SAEs as compared to blacks/African Americans as well as in non-Hispanic/Latinos as compared to Hispanic/Latinos. Overall, rates of SAEs in these subpopulations were low and the significance of the observed trends is uncertain. No large differences in the overall rate of SAEs between sexes or in the rates of death among any of the subpopulations were observed.

Consistent with the results of the efficacy analyses, more IIV4 recipients had medically-attended "ILI" as compared to Flublok RIV4 recipients (0.3% vs 0.1%). MAEs were otherwise similar between treatment groups. Subpopulation analyses in both treatment groups revealed a trends towards more MAEs among females than males, whites/Caucasians than blacks/African Americans, and non-Hispanic/Latinos than Hispanic/Latinos. The largest imbalances were observed in the SOC categories of Infections and Infestations, Respiratory, Thoracic, and Mediastinal Disorders, and General Disorders and Administration Site Conditions, without notable imbalances for specific preferred terms, including influenza or ILI. The study was not powered to draw definitive conclusions from the data.

AESIs and potential hypersensitivity type events were uncommon, non-serious, mostly mild to moderate, and generally balanced between treatment groups. No severe or serious allergic reactions to Flublok occurred post-vaccination. Flublok RIV4 was not associated with a greater risk of acute hypersensitivity in this population of adults ≥50 years of age.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The application contained data from two studies conducted in different age groups, 18-49 years and ≥50 years of age, known to have different immune responses and safety profiles following vaccination. Additionally, PSC12 evaluated clinical endpoint data with immunogenicity from only a small subgroup while PSC16 contained solely immunogenicity data. Therefore, integrated analyses of efficacy and safety were not conducted and these data will be presented separately for each age group in the PI. Please see Section 6 for individual study data.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The application contained data from two studies conducted in different age groups, 18-49 years and ≥50 years of age, known to have different safety profiles following vaccination. Therefore, integrated analyses of safety were not conducted and these data will be presented separately for each age group in the PI. Please see Section 6 for individual study data.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

In response to a request for information (STN 125285/194.22), the Applicant indicated that eight female subjects, seven Flublok RIV4 and one IIV4 recipient, became pregnant during PSC16. All had negative screening urine pregnancy tests and became pregnant following exposure to study vaccine. Information was not sufficient to estimate the time of conception in relation to vaccinations. One Flublok RIV4 recipient, Subject ID (b) (6) , had a spontaneous abortion 68 days post-vaccination (please see Section 6.1.12.4, non-fatal SAEs, for details). One Flublok RIV4 and one IIV4 recipient were lost to follow-up and the outcome of their pregnancies unknown. The remaining five Flublok RIV4 recipients delivered full term healthy infants.

No adequate and well-controlled studies of Flublok, trivalent or quadrivalent formulations, have been conducted in pregnant or lactating females. At the time this review was completed, a pregnancy registry (a PMC associated with the original approval of Flublok) had not been initiated. Available data from clinical trials and postmarketing reports are insufficient to draw conclusions regarding the safety and efficacy of Flublok in pregnant or lactating females. Reproduction studies of Flublok (trivalent formulation) in rats at approximately 300 times the human dose have demonstrated no adverse effects on mating, female fertility, pregnancy, parturition, lactation, embryo-fetal or pre-weaning development, and was not associated with vaccine-related fetal malformations or evidence of teratogenicity.

9.1.2 Use During Lactation

Please see Section 9.1.1.

9.1.3 Pediatric Use and PREA Considerations

Flublok was approved in adults 18-49 years on January 16, 2013 and in adults ≥50 years on October 29, 2014. Flublok is not approved in the pediatric population. In accordance with the Pediatric Research Equity Act regulations, the original approval of Flublok was associated with two deferred postmarketing requirements (PMRs) to conduct studies to evaluate the safety and immunogenicity of Flublok in children and adolescents 6 through 17 years of age (PSC08) and in children 3 through 5 years of age (PSC14). In October 2014, PSC initiated clinical development of a quadrivalent formulation under IND 15784, which triggered PREA due to the new active ingredient, and submitted an initial Pediatric Study Plan (iPSP) for Flublok RIV4. In response to our

advice regarding their proposed pediatric study protocols, PSC revised study PSC08 into two PMR studies, an exploratory Phase 2 study (PSC08) and a Phase 3 study (PSC17), both in children and adolescents 6 through 17 years. The Pediatric Review Committee (PeRC) concurred with the agreed iPSP in on May 14, 2014. PSC submitted the final study report for PSC08 to STN 125285/192 on November 16, 2015. A clinical review determined that the study fulfilled this PREA PMR. On February 2, 2016, CBER issued a letter to PSC releasing the Applicant from the original single PMR study PSC08, and then re-issued the original PMR in children and adolescents 6 through 17 years as two PMRs, PSC08 and PSC17.

The current efficacy supplement has triggered PREA because it contains a new active ingredient, a second influenza B virus recombinant hemagglutinin. The sponsor submitted a final PSP to STN 125285/194 that included three deferred studies, PSC08, PSC17, and PSC14. Studies in children <3 years were waived because evidence from PSC02, a 2004-2005 study of safety and immunogenicity in children 6 through 59 months, demonstrated markedly diminished immunogenicity in this population as compared to Fluzone, strongly suggesting that Flublok would be ineffective in this age group. The PeRC approved the PSP on March 9, 2016. However, on March 22, 2016, PSC submitted a meeting request to discuss a revised pediatric plan which proposed conducting a single clinical endpoint study of the relative VE of Flublok RIV4 in children 3 through 17 years in Mexico as compared to a U.S.-licensed IIV4. This plan was acceptable to the review team, and the Approval Letter for Flublok Quadrivalent will release PSC from the current PSC17 and PSC14 PMRs and re-issue PSC17 as a new PMR to evaluate the safety, immunogenicity and efficacy of Flublok Quadrivalent in children 3 through 17 years.

The deferred pediatric PMR study, PSC17, is as follows:

PSC17, a Phase 3 study to evaluate the safety, immunogenicity, and efficacy of a Flublok quadralent formulation in children ages 3 years through 17 years.

- Final Protocol Submission: January 31, 2018
- Study Completion Date: June 30, 2019
- Final Report Submission: June 30, 2020

9.1.4 Immunocompromised Patients

Information regarding the safety and effectiveness of Flublok in immunocompromised individuals is not sufficient to support specific recommendations in this population.

9.1.5 Geriatric Use

The trivalent formulation of Flublok was granted accelerated approval in adults ≥50 years on October 29, 2014 based on acceptable safety data and non-inferior GMT ratios as compared to Fluzone. Please refer to STN 125285/78 for details of the studies supporting initial licensure. Data from PSC12 were submitted to this efficacy supplement to support traditional approval in adults ≥50 years. Please see Sections 6, 10, and 11 of this review.

10. CONCLUSIONS

In adults 18-49 years (PSC16), Flublok RIV4 demonstrated acceptable safety and met pre-specified success criteria for the primary immunogenicity endpoint of non-inferior post-vaccination GMTs and SCRs relative to IIV4 for both influenza A strains and for B/Yamagata but not for the B/Victoria lineage strain. The reasons for lower immunogenicity against the B/Victoria virus are not completely clear. A study population immunologically naïve to influenza B viruses, particularly to the B/Victoria lineage, may partially explain these findings and is supported by the low baseline and post-vaccination GMTs in both treatment groups. Other potential explanations may include use of whole virus and/or egg-derived antigens in the HI assay. While low responses to influenza B have also been observed in some studies of other influenza vaccines, others have demonstrated robust responses to the B strains that were higher than for the A strain components. Future studies, perhaps in the pediatric population, may provide an opportunity to examine whether low immune responses to BVictoria relative to B/Yamagata or in recipients of Flublok RIV4 relative to IIV4 are reproducible, and may provide additional insights.

In adults 50 years and older (PSC12), Flublok RIV4 demonstrated acceptable safety and met pre-specified success criteria for the primary endpoint of non-inferior vaccine efficacy relative to IIV4 [rVE 30% (95% CI: 10%, 47%)] against rt-PCR-confirmed protocol-defined ILI due to all strains. Subanalyses and exploratory analyses suggest that Flublok had greater efficacy than IIV4 against a predominant and (presumed) antigenically distinct A/H3N2 virus. Although we do not know how these results translate to absolute VE for Flublok, demonstrating greater rVE against what were probably predominantly antigenically mismatched A/H3N2 viruses is a significant benefit and a more difficult threshold to reach than demonstrating non-inferior VE against antigenically similar viruses. Nevertheless, some uncertainties in the clinical significance of the results to consider include:

- Unusually low vaccine effectiveness of the class of IIVs (likely including the Fluarix QIV comparator), well-documented by the CDC Influenza Vaccine Effectiveness Network observational study during the study period, and previous data (documented in the Fluarix PI) showing a trend towards a very low VE for Fluarix TIV in a subset of adults 50-64 years of age (in contrast to subjects 18-49 years);
- Lower and inconclusive rVE against influenza B strains [rVE 4% (95% CI: -72%, 46%)] coupled with very low immunogenicity against the B/Victoria lineage virus that failed to demonstrate non-inferiority versus IIV4;
- Failure to demonstrate a non-inferior SCR for A/H1N1 and absent rVE data for this strain;
- Results driven by adults 50-64 years and subanalyses showing trends towards lower rVE and immunogenicity for Flublok RIV4 in adults ≥65 years.

Because an accurate assessment of VE depends on many changing variables and requires multiple years of study, there is some inherent uncertainly in estimating the effectiveness of influenza vaccines from season to season. Similar issues of concern relating to effectiveness against influenza B and in the elderly have been raised for other influenza vaccines. Additionally, subanalyses by influenza strains and age groups represent trends to potentially explore further but do not allow definitive conclusions.

Given these considerations, the reviewer concludes that Flublok RIV4 was at least 10% (95% CI: 10%, 47%) more efficacious in preventing influenza illness due to a predominant antigenically mismatched A/H3N2 virus (generally considered more virulent than A/H1N1 or B strains) than a currently U.S-licensed QIV in adults ≥50 years, and demonstrated acceptable immunogenicity and safety relative to Fluarix QIV in adults ≥18 years. These data support traditional approval of Flublok RIV4 in adults ≥18 years.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 44: Risk-Benefit Considerations – Flublok Quadrivalent		
Decision Factor	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Influenza causes annual epidemics affecting 5-20% of the population each year. Due to frequent mutations and reassortment, antigenic drift and shift, in viral envelope glycoproteins (HA and NA), the extent and severity of seasonal epidemics are variable and unpredictable. • In the US, annual influenza-associated respiratory and circulatory mortality rates ranged from 3,349 to 48,614 (average 23,607) from 1976-2007. Hospitalizations ranged from 55,000 to 431,000. Complications disproportionately affect persons < 2 years and ≥65 years of age and persons with underlying cardiac, respiratory, metabolic, or immune compromising medical conditions. However, antigenic shifts may cause pandemics that also result in significant mortality among healthy children and young adults. • Since 1985, two genetically distinct B virus lineages have co-circulated and comprise ~ 25% of isolates in the US. During the ten seasons from 2001-2002 through 2010-2011, prediction of which B lineage would predominate was correct for only five seasons, resulting in a mismatch between the vaccine and the circulating strain for 50% of the 10 year period. The CDC estimated that in a season where there is a B strain mismatch, the availability of a quadrivalent vaccine could result in an annual reduction of 2,200-970,000 influenza cases, 14-8,200 hospitalizations, and 1-485 deaths.	• Influenza is a serious, sometimes life-threatening disease. Persons of all ages are at risk for significant morbidity and mortality. • Protection requires annual vaccination with a formulation containing virus strains predicted to circulate during each season. • Illnesses caused by influenza B viruses represent a considerable proportion of overall influenza disease burden. Vaccine coverage of both B strains is desirable, particularly in young children who experience the highest mortality due to B strains (~34-38% of pediatric deaths reported to CDC from 2004-2011 were due to influenza B). • In 2013, the World Health Organization (WHO) and the VRBPAC recommended the inclusion of a second influenza B vaccine virus antigen in quadrivalent influenza vaccines to provide coverage for both B lineages concurrently.
Unmet Medical Need	• Five antiviral agents are licensed in the US for the prevention or treatment of influenza in persons with severe, complicated, or progressive disease, or who are at higher risk for complications. Two adamantane agents are active only against influenza A and are no longer recommended because of widespread resistance. Neuraminidase inhibitors are also limited by emergence of resistance (primarily to type A viruses) and adverse reactions. • Licensed influenza vaccines available in the United States (2015-16 season) include: six trivalent (Afluria, Fluarix, FluLaval, Fluviron, Fluzone, and Flucelvax) and five quadrivalent (Afluria, Fluarix, FluLaval, Fluzone, and Fluzone intradermal) inactivated influenza vaccines (TIV and QIV), a trivalent recombinant influenza vaccine (Flublok), and a live-attenuated influenza vaccine (LAIV4, FluMist Quadrivalent). To improve immunogenicity, one high dose TIV (Fluzone HD) and one adjuvanted TIV (Fluad) are also licensed in the elderly. • Approximately 148 million doses of influenza vaccine were distributed in the US in the 2014-2015 season. Influenza vaccine coverage rates are relatively stagnant and remain below the DHHS Healthy People 2020 targets of 80% in persons 6 months through 64 years of age and 90% in persons ≥65 years of age. Although this does not appear to be due to a shortage of vaccine, the doses of vaccine distributed for the 2014-2015 influenza season are less than the population for whom the vaccine is indicated. • Flublok is the only influenza vaccine manufactured without the use of eggs. However, the risk of anaphylaxis following egg-based IIVs is rare (~0.5-2.0%). Several studies have clearly demonstrated that the risk of allergic reactions, including anaphylaxis, following administration of	• Immunoprophylaxis is the preferred method of controlling influenza. The CDC recommends annual influenza immunization for all persons ≥6 mos of age with no contraindications to vaccination. • Antivirals are important adjuncts for treatment and prevention of influenza but are not substitutes for vaccination. • Currently licensed influenza vaccines are effective against antigenically matched strains, and are well tolerated. When vaccine and circulating viruses are well-matched, vaccination with TIV is ~70-90% effective in preventing influenza illness among young healthy adults < 65 years of age. • Inclusion of both B lineages as part of a quadrivalent vaccine is projected to provide additional benefit in most seasons and is likely to become the standard of care. • An additional licensed QIV will be beneficial given the transition from TIV to QIVs and targeted coverage.

	egg-based IIVs is no greater in egg-allergic individuals than in those without egg allergy. Experts increasingly recognize the safety of egg-based IIVs even in patients with severe egg allergy.	• Absence of egg protein in Flublok does not represent a major benefit over egg-based IIVs.
Clinical Benefit	• In a randomized, controlled trial (RCT) of 9003 adults ≥50 years (PSC12), vaccination with Flublok Quadrivalent (RIV4) was associated with a 30% (95% CI: 10%, 47%) lower relative risk of rt-PCR-confirmed influenza illness (due to all strains) as compared to Fluarix QIV, meeting prespecified criteria for non-inferior relative vaccine efficacy (rVE) and exploratory criteria for superiority. Post-hoc analyses revealed a rVE of 36% (95% CI: 14%, 53%) for influenza A/H3N2 and 4% (95% CI: -72%, 46%) for influenza B. The 2014-15 influenza season was characterized by an antigenically mismatched, predominant A/H3N2 virus. B/Yamagata and, to a lesser extent, B/Victoria viruses co-circulated later in the season and were antigenically similar to the vaccine antigens. Subanalyses by age revealed an rVE of 41% (95% CI: 15%, 61%) for adults 50-64 years (59.7% of the Efficacy Population) and 17% (95% CI: -20%, 43%) for adults ≥65 years (40.3% of the EP). An immunogenicity subset of subjects vaccinated with Flublok RIV4 (n=317) met pre-specified co-secondary endpoint criteria for non-inferior HI GMT ratios and SCR differences as compared to Fluarix QIV (n=300) for the A/H3 and B/Yamagata vaccine antigens, but failed to meet criteria for the SCR difference for A/H1 and failed both the SCR difference and GMT ratio for B/Victoria. Uncertainties related to this trial include the clinical significance of being NI to a comparator that probably had unacceptably low vaccine effectiveness based on a case control test negative observational study by the CDC during the study period, and also based on prior VE data for Fluarix TIV reviewed by FDA and published in the PI [absolute VE of 13.8% (LB 95% CI: -137%) in a subanalysis of adults 50-64 years; subanalysis was not powered for hypothesis testing but is trending in the wrong direction]. Although the purpose of including a second B antigen is to increase protection against influenza B, the effectiveness of Flublok RIV4 against influenza B appears less certain than effectiveness against A/H3N2 because of the inconclusive trends revealed by rVE subanalyses and low immune responses to the B antigens observed in the immunogenicity subset. • Age group subanalyses in PSC12 showed a trend towards lower rVE for Flublok RIV4 in adults ≥65 years and did not meet criteria for NI although the subanalyses lacked statistical power. A trend towards lower SCRs and GMTs and higher SCR differences and GMT ratios (i.e., not non-inferior to IIV4) was observed in adults ≥65 years for A/H1N1 and in adults ≥75 years for A/H1N1, A/H3N2, and B/Yamagata. B/Victoria failed NI criteria in all age subgroups. Subanalyses of rVE and immunogenicity by sex, race, and ethnicity showed trends similar to the overall study population. • In a RCT of 1350 adults 18-49 years (PSC16), vaccination with Flublok RIV4 elicited an immune response that met pre-specified HI GMT and SCR co-primary endpoints and success criteria for non-inferior GMT ratios and SCR differences for three of four vaccine virus antigens (A/H1, A/H3, and B/Yamagata) as compared to U.S.-licensed Fluarix RIV4. The B/Victoria antigen failed to demonstrate a non-inferior immune response. Subpopulation analyses by sex, race, and ethnicity showed trends similar to the overall population. The numbers of subjects representing racial groups other than blacks or whites were too small to draw meaningful conclusions. • Clinical benefit in adults 18-49 years was inferred from Flublok (trivalent), manufactured by the same process as Flublok RIV4.	• Flublok RIV4 demonstrated non-inferior VE relative to Fluarix QIV, a U.S.-licensed vaccine in an appropriately designed trial in adults ≥50 years (PSC12). Exploratory and subanalyses also suggested that Flublok had greater efficacy than IIV4 in preventing illness due to A/H3N2 viruses that were probably mostly antigenically distinct from vaccine antigens. Although it is uncertain how these results translate into absolute VE, demonstration of efficacy against mismatched strains is more difficult than showing efficacy against matched strains. • Flublok RIV4 demonstrated non-inferior immunogenicity relative to Fluarix QIV for 3 of 4 vaccine antigens in adults 18-49 years in an appropriately designed trial (PSC16). For reasons that are not clear, Flublok Q did not elicit non-inferior immune responses to the B/Victoria antigen, however, the immunogenicity of both vaccines was low. Other influenza vaccines have elicited low immune responses to B antigens. • The rVE results in adults ≥50 years may not be generalizable to other comparator vaccines, seasons with better antigenic matching of comparator vaccines, or to seasons where B strains are more prevalent. These uncertainties are of particular concern in the elderly subpopulation ≥65 years of age which is also at greater risk for serious complications of influenza. However, because an accurate assessment of VE depends on many changing variables and requires multiple years of study, there is inherent uncertainly in evaluating the effectiveness of influenza vaccines. • Because the original approval of Flublok in adults 18-49 years (PSC04) was based on a lower absolute VE than is normally accepted [44.8% (95% CI: 24.4%, 60%)], the intent of the PSC12 PMR was to collect more robust and conclusive clinical endpoint data for this vaccine. PSC declined our advice to extend PSC12 to a second season. 2015-16 was characterized by predominant and well-

	• Although generally less severe than type A, influenza B causes significant and serious disease, particularly in young children. The inability to predict which lineage will circulate in a given season is the basis for development of quadrivalent influenza vaccines. Based on the results of PSC12 and PSC16, the clinical efficacy and effectiveness of Flublok RIV4 against influenza B remains uncertain, in the opinion of this reviewer, although the results may be explained in part by immunologically naïve study populations. • Flublok is still a relatively novel vaccine. Unlike whole virus or split virion vaccines, it contains no neuraminidase (NA) or internal core proteins (e.g., nucleoprotein, M protein). Antibodies to NA may lessen the severity of illness and correlate with protection independent of anti-HI antibodies. CMI induced by internal proteins is thought to contribute to protection, particularly in the elderly. • Flublok RIV4 contains 3x more HA antigen than IIV4. Flublok HI GMTs were higher than IIV4against A/H3 in adults ≥50 years and against A/H1 and A/H3 in adults 18-49 years. Some studies have shown an association between higher GMTs and greater protection against illness.	matched A/H1N1 and B strains, and may have provided additional insights regarding efficacy. • Despite some uncertainty over the effectiveness of Flublok RIV4 against influenza B and in the elderly, similar uncertainties exist for other licensed IIVs, and rVE data from PSC12, like PSC04, demonstrate clinical efficacy against presumed antigenically mismatched A/H3N2. Protection against antigenically mismatched virus and the more virulent A/H3N2 subtype is a clear benefit of Flublok. • Subpopulation analyses by age represent trends but do not allow definitive conclusions.
Risk	• In both adults 18-49 years and ≥50 years, the most common adverse events following vaccination with Flublok RIV4 were mild to moderate local injection site tenderness and pain, headache, fatigue, muscle pain, and joint pain. Adults ≥50 years of age reported less reactogenicity than younger subjects. Most events resolved within 2 days. In both age groups, rates of solicited local and systemic AEs were similar between recipients of Flublok RIV4 and IIV4 except for slightly more injection site redness in younger Flublok RIV4 recipients. Rates of severe events were low, non-serious, and self-limited. • In adults 18-49 years (PSC16), ten (1%) Flublok RIV4 but no IIV4 recipients were identified as having potential hypersensitivity type AEs such as bronchospasm, pruritus, or rash in the five days post-vaccination, or diarrhea within two days of vaccination. Most events were mild and non-serious, and, for many of the events, causality uncertain. One AE of bronchospasm three days following Flublok RIV4 was moderate to severe. In adults ≥50 years, potential hypersensitivity type AEs were uncommon and balanced between treatment groups (<0.5% regardless of attribution). Among Flublok RIV4 recipients ≥50 years, the following events may have represented hypersensitivity and may have been related to vaccination: severe headache and vomiting, presyncope, “allergy”, pruritus, hives, vomiting, and diarrhea. One IIV4 recipient had a severe “drug eruption” two days post-vaccination. No other severe or serious allergic reactions were reported. • No unusual unsolicited AEs, large imbalances, or trends were observed in adults ≥18 years of age. Deaths and SAEs were balanced between treatment groups in both studies. None appeared clearly related to study vaccines. • Subpopulation analyses showed a trend towards more solicited and unsolicited AEs in females vs males in both treatment and age groups. In adults 18-49 years, whites and non-Hispanic/Latinos reported more local injection site reactions than blacks/African Americans or Hispanic/Latinos. Among adults ≥50 years, more local injection site reactions were reported among whites, non-Hispanic/Latinos, and adults 50-64 years as compared to blacks/African Americans, Hispanic/Latinos, and adults ≥65 years. No large imbalances in solicited systemic AEs were observed among racial or ethnic groups. In younger adults, 18-49 years, unsolicited AEs were reported more frequently among whites than blacks/African Americans. Among adults ≥50 years, rates of SAEs were higher in females, whites, and non-Hispanic/Latinos as compared to males, non-whites, and Hispanic/Latinos. No subpopulation imbalances in the rates of SAEs were noted in adults 18-49 years. In adults ≥18 years (both studies), more MAEs occurred in females, whites,	• Reactogenicity associated with Flublok RIV4 is acceptable and comparable to IIV4. Available data suggest that the safety profile of Flublok RIV4 with respect to unsolicited and serious AEs, including hypersensitivity, is comparable to U.S.-licensed TIVs and QIVs in adults. • Subpopulation analyses represent trends but do not allow definitive conclusions other than being consistent with previous observations that females generally report more AEs than do males. • Available data for Flublok and Flublok RIV4 are insufficient to inform vaccine-associated risks for adverse pregnancy outcomes. However, inactivated influenza vaccines have a long history of safety and are recommended in pregnant females

	and non-Hispanics/Latinos than in males, non-whites, and non-Hispanic/Latinos. Overall rates of MAEs were lower in adults 18-49 versus ≥50 years. • Safety was not evaluated in pregnant women or nursing mothers.	
Risk Management	• Any potential for increased local and systemic reactogenicity or hypersensitivity associated with Flublok RIV4 can be further described in postmarketing surveillance. • The clinical review team and OBE/DE determined that a neither a safety PMR, REMS nor a Black Box warning were required for Flublok RIV4. • The Applicant will establish a pregnancy registry (PSC15) that will include both recipients of Flublok (trivalent) and Flublok RIV4.	• The known safety profile of Flublok RIV4 will be described in the package insert without the need for a PMR, REMS, or Black Box warning. • Please see the OBE/DE review for details of the postmarketing pregnancy study PSC15.

11.2 Risk-Benefit Summary and Assessment

Flublok RIV4 demonstrated greater vaccine efficacy relative to a currently U.S.-licensed QIV during a season characterized by a predominant antigenically mismatched influenza A/H3N2. This is the second clinical endpoint study demonstrating clinical efficacy against an antigenically distinct (mismatched) wild type A/H3N2 virus. Effectiveness of Flublok RIV4 against influenza B is less certain due to fewer cases in the clinical endpoint study and a rVE of 4% with wide CIs (95% CI: -72%, 46%) in adults ≥50 years as well as lower immunogenicity against both B virus strains not only in older adults but also in adults 18-49 years. Immunogenicity was lower in adults ≥65 years relative to younger adults. The findings of lower effectiveness against influenza B and in elderly adults have also been observed in studies of other influenza vaccines. Nevertheless, we should be careful not to dismiss these findings and remember that 1) immune responses elicited by influenza vaccines against B virus antigens have been inconsistent, with some studies demonstrating robust HI GMTs, and 2) influenza B causes significant and serious disease.

Potential advantages of Flublok RIV4 relative to egg-based influenza vaccines include closer antigenic matching due to recombinant technology which preserves the nucleotide sequence of the HA protein in contrast to propagation in eggs which requires adaptation or reassortant mutations to increase yield. Manufacture is not dependent on availability of eggs and, in the event of a pandemic, has the potential to be increased more quickly than egg-based methods to meet demand, although a higher antigen content (45 µg/antigen) is required to achieve optimal immunogenicity. Regarding the potential advantages of Flublok RIV4 in persons with egg allergy, an increasing body of evidence and societal recommendations support the safety of egg-based influenza vaccines in persons with egg allergy, even in those with a history of anaphylaxis to egg protein. Therefore, in the opinion of this reviewer, the absence of egg proteins in Flublok QIV does not confer significant additional benefit over egg-based IIVs even in most persons with egg allergy.

Overall, the potential benefits of Flublok RIV4 outweigh potential risks and favor approval.

11.3 Discussion of Regulatory Options

Given the antigenic mismatch between vaccine and wild type influenza A/H3N2 and the associated exceptionally low vaccine effectiveness for the 2014-2015 season, CBER had recommended that the Applicant extend PSC12 to a second season to address uncertainties resulting from an ineffective comparator (please see Section 2.5). PSC declined our advice. Please see Sections 11.1 and 11.2. Regulatory options include the following:

- Option #1: Traditional approval in adults 18 years and older. Flublok RIV4 demonstrated greater relative efficacy and higher GMTs against the most virulent strain of influenza, A/H3N2. Approval requires acceptance of a degree of uncertainty regarding effectiveness of Flublok against influenza B/Victoria (and, therefore, the primary rationale for developing a quadrivalent vaccine) and in persons ≥65 years. Absolute VE data (PSC04) from the original approval of Flublok (trivalent formulation) in adults 18-49 provide additional support for approval of the quadrivalent formulation in the young adult population. From a

regulatory view, Flublok RIV4 met the primary endpoint of non-inferior VE against a U.S.-licensed vaccine for the entire study population for whom the study was powered for statistical significance.

- Option #2: Traditional approval of FluBlok Quadrivalent in adults 18-49 years but require further study of vaccine efficacy in adults ≥50 years because clinical benefit is not clearly confirmed in this age subgroup against B/Victoria lineage virus. Clinical endpoint and immunogenicity data in adults 18-49 years are sufficient for influenza A and B/Yamagata but are limited with respect to B/Victoria. However, developing efficacy data against each component of influenza vaccines prior to licensure is difficult due to the inability to predict whether the season of study will be characterized by adequate attack rates, a good antigenic match between vaccine and circulating strains, or sufficient cases of influenza B to yield robust and conclusive data. Although this reviewer prefers Option #2, this was not the option supported by management for the reasons above.
- Option #3: Deny approval in adults ≥18 years. Regarding the entire study population including younger adults 18-49 years, the clinical significance of being non-inferior to a comparator that probably had unusually low vaccine effectiveness during the 2014-2015 influenza season, and the very low immunogenicity of Flublok RIV4 against B/Victoria remain concerns. However, Flublok RIV4's robust immunogenicity against the A/rH3 antigen and 30% rVE against predominantly antigenically mismatched A/H3N2 wild type virus mitigate against these concerns.

11.4 Recommendations on Regulatory Actions

The reviewer recommends approval with some reservations regarding the effectiveness of Flublok against influenza B/Victoria and in the elderly while acknowledging that influenza vaccine effectiveness depends on multiple variables that change from one season to the next, that no single season provides conclusive data, and that some degree of uncertainty is unavoidable.

11.5 Labeling Review and Recommendations

Labeling negotiations were ongoing at the time this review was completed. Because data from PSC12 will be used to grant traditional approval for both Flublok Quadrivalent and Flublok (trivalent formulation) in adults ≥50 years, in addition to submitting a draft Package Insert (PI) for Flublok Quadrivalent, CBER asked PSC to submit a revised PI for Flublok (trivalent formulation) updated with efficacy data from PSC12. Major changes to the Applicant's draft PIs and areas of negotiation were:

<u>Flublok Quadrivalent</u>

- Clinical Trials Experience [6.1]: In addition to new data from PSC12 and PSC16, death and SAE data from the trivalent safety database were included.
- Pregnancy [8.1] and Lactation [8.2]: Modified to conform to the new PLLR.
- Geriatric Use [8.5]: A statement regarding the rVE data from PSC12 replaced a statement regarding immunogenicity data from studies of the trivalent formulation.

<u>Flublok (trivalent formulation)</u>

- Highlights, Indications and Usage [1]: Removed a statement that the indication in adults ≥50 years was based on the immune response elicited by Flublok.

- Clinical Trials Experience [6.1]: PSC was offered an option to include death and SAE data from PSC12 and PSC16 in this section.
- Pregnancy [8.1] and Lactation [8.2]: Modified to conform to the new PLLR.
- Geriatric Use [8.5]: A statement regarding the rVE data from PSC12 replaced a statement regarding immunogenicity data from studies of the trivalent formulation.
- Clinical Studies [14]: Updated with efficacy data from PSC12.

In addition to the above revisions, the review team engaged in internal discussions with management regarding inclusion of a statement in both PIs informing the reader that postmarketing reports of severe and serious allergic reactions following Flublok include reactions among persons with self-reported histories of egg allergy and/or allergic reactions to previous influenza vaccination. The clinical review team and OBE/DE recommended a more specific and visible warning than was contained in the draft PIs for the following reasons: 1) most postmarketing reports of severe or serious allergic reactions to Flublok have occurred in persons with a history of allergic reactions to egg or to previous egg-based influenza vaccination; 2) a substantial body of literature now supports the safety of egg-based influenza vaccines in persons with egg-allergy, including those with anaphylaxis; 3) persons with a history of allergic reactions to influenza vaccines are likely to be atopic and may react to non-egg protein components of influenza vaccines, potentially including components of Flublok or Flublok Quadrivalent; and 4) PSC markets Flublok for use in persons with histories of allergic reactions to eggs or egg-based influenza vaccines, suggesting that Flublok is safer in these individuals. The outcome of our internal discussions was that management determined that the current Flublok trivalent and draft quadrivalent PIs were adequate in describing the possibility of severe allergic reactions following Flublok and Flublok Quadrivalent, and do not need a qualifier to the Contraindications, Warnings and Precautions, or Postmarketing Experience sections of the PIs.

Please refer to the final versions of the PIs, available in the EDR.

11.6 Recommendations on Postmarketing Actions

Pediatric Postmarketing Requirements (PMRs) to fulfill PREA
Please see Section 9.1.3.

Postmarketing Commitments (PMCs)
Study PSC13, a PMC associated with the original approval of Flublok (trivalent formulation), is an observational retrospective cohort study that will further characterize the safety of Flublok as compared to egg-based IIVs. The Applicant indicated that PSC13 has almost reached its targeted enrollment of approximately 25,000 Flublok recipients, and that they do not plan to enroll recipients of Flublok RIV4. Because the clinical trial data did not demonstrate major differences in adverse events between Flublok RIV4 and IIV4, the review team agreed that routine postmarketing surveillance for Flublok RIV4 was acceptable. However, if PSC13, postmarketing safety surveillance, or other sources of data suggest a signal of serious risk or potential for serious risk, then OBE/DE may recommend a phase 4 study to evaluate the safety of Flublok RIV4. Please see the OBE/DE review for further discussion.

Pregnancy Registry

At the time of approval of this supplement, PSC15, a pregnancy registry and PMC to which the Applicant agreed under the original Flublok approval, had not yet been initiated. In response to our March 7, 2016 request for information (STN 125285/217), PSC indicated that the registry would be managed by a CRO with appropriate expertise and would include pregnant female exposures to both Flublok (trivalent) and Flublok RIV4. Please see the OBE/DE review for additional information.