Summary Basis for Regulatory Action

Date: October 7, 2016

From: Timothy A. Fritz, PhD, Review Committee Chair

BLA/ STN#: 125285/194

Applicant Name: Protein Sciences Corporation

Date of Submission: December 8, 2015

PDUFA Goal Date: October 7, 2016

Proprietary Name/ Established Name: Flublok Quadrivalent, Influenza Vaccine

Indication: Prevention of influenza disease in persons 18 years of age and older caused by influenza virus subtypes A and types B contained in the vaccine.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, MD, Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Specific documentation used in developing the SBRA	**Reviewer – Date of Review**
Clinical Review	Cynthia Nolletti, MD – 04 October 2016
Statistical Review	Rong Fu, PhD – 01 September 2016
Bioassay Statistical Review	Rong Fu, PhD – 09 September 2016
Pharmacovigilance Review	Emily Jane Woo, MD, MPH – 02 June 2016
CMC/Product Review	Maryna Eichelberger, PhD – 04 October 2016
CMC/Facilities and Equipment	Lori Peters, MS – 03 October 2016
Labeling Reviews	Cynthia Nolletti, MD – 04 October 2016 Emily Jane Woo, MD, MPH – 02 June 2016 Sonny Saini, PharmD – 23 August 2016 Daphne Stewart – 15 September 2016
Testing Methods and Analytical Chemistry Reviews	Manju Joshi, PhD – 23 August 2016 Alfred Del Grosso, PhD – 07 September 2016 Hyesuk Kong, PhD – 15 June 2016, 12 August 2016
Bioresearch Monitoring Review	Colonious King – 07 September 2016

1. Introduction

Flublok® Quadrivalent is a vaccine manufactured by Protein Sciences Corporation (PSC) for the active immunization of persons 18 years and older for the prevention of influenza disease caused by influenza virus subtypes A and types B contained in the vaccine. Compared to Flublok®, Flublok Quadrivalent contains an additional rHA antigen from a type B influenza virus. The presence of the two B-type virus antigens in quadrivalent influenza vaccines is intended to provide protection against both B/Yamagata and B/Victoria lineage influenza viruses. The vaccine is formulated as a sterile, aqueous, buffered solution of four purified, recombinant influenza hemagglutinins (rHAs) and contains no egg proteins. The four rHAs are produced in *Spodoptera frugiperda* insect cells using a Baculovirus Expression Vector System (BEVS) in which the cells are infected with a baculovirus engineered to contain the gene for the corresponding influenza HA antigen. Each 0.5 mL dose of Flublok Quadrivalent contains 180 mcg of rHA antigens (45 mcg each of H1, H3, B/Victoria and B/Yamagata rHAs) and may contain residual amounts (≤ 19 mcg) of baculovirus and insect cell proteins.

CBER received supplement STN 125285/194 on 08 December 2015 with efficacy, immunogenicity and safety data from a required postmarketing study (PSC12) to verify clinical benefit, a condition of accelerated approval specified in the 29 October 2014 approval letter granting licensure for the use of the Flublok trivalent formulation in persons aged 50 years and older (STN 125285/78). Data from PSC12 were also used to support licensure of Flublok Quadrivalent in this population. Immunogenicity and safety data from a second study, PSC16, were included to support the use of Flublok Quadrivalent in persons 18-49 years of age. Data were also provided to support licensure of a new contract facility (b) (4) used to formulate and fill Flublok Quadrivalent into single-dose syringes.

2. Background

Flublok (trivalent formulation) was licensed in the United States on 16 January 2013 (STN 125285/0) for persons 18-49 years of age. Accelerated approval was granted on 29 October 2014 (STN 125285/78) to extend the use of Flublok to persons 50 years of age and older and was based on safety and non-inferior immunogenicity results from three clinical studies. At CBER's request, PSC agreed to conduct a clinical endpoint study in persons 50 years and older to support traditional approval due to more limited data relating hemagglutination inhibition (HI) antibody titers from non-egg based vaccines with protective immunity. To fulfill the accelerated approval requirement to confirm clinical benefit, it was agreed that PSC could use a quadrivalent formulation of Flublok (Flublok Quadrivalent) in the study in persons 50 years of age and older (PSC12). PSC12 was a Phase 3, relative vaccine efficacy, immunogenicity and safety clinical trial. PSC also conducted a Phase 3, non-inferior immunogenicity and safety study (PSC16) to support the licensure of Flublok Quadrivalent in persons 18-49 years of age.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The four Flublok Quadrivalent rHA monovalent bulk drug substances used to produce Flublok Quadrivalent Drug Product are manufactured using the same process licensed for the manufacture of Flublok (STN 125285/0).

Drug Substance

PSC's Meriden, CT and Pearl River, NY facilities are licensed to manufacture Flublok monovalent bulk Drug Substance (DS) under STN 125285/0 and 125285/127. Working cell banks of *expres*SF+ *Spodoptera frugiperda* insect cells are grown in serum-free medium and expanded in (b) (4) culture. To express the rHA, the (b) (4) culture is infected with a baculovirus engineered to contain the gene for the viral hemagglutinin protein. Following expression, the cells are harvested by (b) (4) and solubilized with a detergent solution to extract the rHA. (b) (4) chromatography columns to purify the rHA. (b) (4) and the purified rHA is (b) (4) to produce monovalent bulk rHA DS. Monovalent bulk DS release testing is performed at the Meriden, CT facility and at (b) (4).

Drug Product

Monovalent bulk DS is shipped from Pearl River, NY or Meriden, CT to (b) (4) to formulate and fill Flublok Quadrivalent Drug Product (DP) into single-dose syringes. The DS used in Flublok Quadrivalent manufacture validation studies were rHAs from viruses recommended for 2015/16 quadrivalent influenza vaccines: A/California/7/2009 (H1N1), A/Switzerland/9715293/2013 (H3N2), B/Phuket/3073/2013 (a B/Yamagata-lineage virus) and B/Brisbane/60/2008 (a B/Victoria-lineage virus). Formulation and filling data from 3 validation lots ((b) (4)) demonstrated that the viruses are adequately mixed within (b) (4) and the formulated bulk can be held for up to (b) (4). A (b) (4) . The quadrivalent formulated bulk is (b) (4) and then filled into single dose glass syringes in the filling area. Data were provided to demonstrate the product is consistently filled into the syringes.

Drug Product is shipped from (b) (4) to Meriden, CT where most release testing is performed. Sterility release testing is contracted to (b) (4) . Minor changes were made to some DP release specifications to account for the addition of the second B-type influenza antigen. Stability data provided in the supplement support a 6 month shelf-life for Flublok Quadrivalent when stored at 2-8°C. The date of manufacture is designated as the date the formulated bulk is sterile filtered and filled into the final container.

The presence of two B-type influenza antigens in quadrivalent influenza vaccines required a modification to the Single Radial Immunodiffusion (SRID) assay to ensure proper measurement of the potency of the individual B-type antigens. CBER's review concluded that PSC appropriately revised and validated their SRID assay.

Three Flublok Quadrivalent DP process validation lots ((b) (4)) were submitted for CBER testing in support of the supplement. CBER's potency test results for the B/Brisbane/60/2008 antigen of lots (b) (4) and (b) (4) were more than 20% lower than PSC's results prompting CBER to request that PSC conduct a root cause investigation. The discrepancy was determined to have several causes, including differences in the operating parameters of the SRID assays between the CBER and PSC laboratories, and the loss in DP potency that occurred between testing by PSC and CBER. To prevent the recurrence of discrepant results, PSC agreed to align their assay with CBER's assay and potency testing will be coordinated to ensure that CBER testing occurs within 1 week of PSC testing. CBER confirmed that implementing these measures will reduce SRID assay result differences between CBER and PSC.

b) CBER Lot Release

A review of Product Release Branch records indicate that there are no pending lots or issues that would affect approval of the submission. Revisions to the Lot Release Protocol template submitted by PSC were found to be acceptable.

c) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Flublok Quadrivalent are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Manufacturing Facilities Table for Flublok Quadrivalent

Name/address	FEI number	Inspection/ waiver	Results/ Justification
Drug substance manufacturing, release and stability testing of drug product, lot release of drug product Protein Sciences Corporation 1000 Research Parkway Meriden, CT 06450	1221506	Waived	Team Biologics June 2016 VAI
Drug substance manufacturing Protein Sciences Corporation 401 North Middletown Road Pearl River, NY 10965	3011286996	Waived	CBER/DMPQ March 2015 VAI

Name/address	FEI number	Inspection/ waiver	Results/ Justification
Drug product manufacturing including formulation, syringe fill/finish, in-process testing, labeling, and packaging (b) (4)	(b) (4)	PAI	(b) (4) VAI
General safety and sterility release testing for drug product (b) (4)	(b) (4)	Waived	(b) (4) NAI
(b) (4)	(b) (4)	Waived	(b) (4) NAI

VAI – Voluntary Action Indicated, NAI – No Action Indicated

Team Biologics performed a surveillance inspection from June 8 – 15, 2016 of Protein Sciences Corporation's drug substance manufacturing facility in Meriden, CT. The corrective actions to the observations were deemed satisfactory by Team Biologics and the inspection was classified as voluntary action indicated (VAI).

CBER/DMPQ performed a pre-approval inspection from March 2 – 6, 2015 of Protein Sciences Corporation's drug substance manufacturing facility in Pearl River, NY under Prior Approval Supplement STN 125285/127. All 483 issues were resolved and the inspection was classified as VAI.

CBER/DMPQ performed a pre-approval inspection from (b) (4) of (b) (4) in (b) (4), the contract manufacturer responsible for the drug product manufacturing activities, including filling of Flublok Quadrivalent drug product into syringes. The inspection was classified as VAI and all inspectional observations have been satisfactorily resolved.

ORA performed surveillance inspections of (b) (4) drug product testing locations in (b) (4) and (b) (4) in (b) (4) and (b) (4), respectively. The inspections were both classified as no action indicated (NAI).

d) Environmental Assessment

The BLA included a request for categorical exclusion from an environmental assessment under 21 CFR 25.31 (c). The FDA concluded that this request is justified as the manufacturing of Flublok Quadrivalent will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Container Closure System

The drug product is filled into a 1mL (b) (4) glass syringe supplied by (b) (4) which is configured with a Luer-lock for needle attachment and has a (b) (4). The syringes are provided needleless and the needle size is selected by the healthcare provider administering the vaccine. The tip caps are an (b) (4) and are supplied by (b) (4). The bromobutyl stopper is supplied by (b) (4). The plunger rods are manufactured by (b) (4) and are composed of (b) (4). (b) (4) is responsible for (b) (4), and sterilizing the components of the container closure system.

Container closure integrity testing of the syringes was performed by (b) (4) using the (b) (4) test method; all acceptance criteria were met.

4. Nonclinical Pharmacology/Toxicology

A developmental toxicity study was conducted for Flublok (trivalent formulation) and reviewed under STN 125285/0. Nonclinical pharmacology/toxicology data were not provided in this supplement because CBER advised PSC under IND 15784 that this data would not be needed due to the similarity of Flublok Quadrivalent to Flublok.

5. Clinical Pharmacology

No new clinical pharmacology data was required in support of this supplement.

6. Clinical/ Statistical

a) Clinical and Statistical Summary of Efficacy and Immunogenicity Results

The safety, immunogenicity and efficacy of Flublok Quadrivalent were evaluated in persons ≥ 18 years old in two clinical studies, PSC12 and PSC16. A U.S.-licensed, quadrivalent inactivated influenza vaccine, Fluarix® Quadrivalent (IIV4, GlaxoSmithKline) was used as the active comparator in each study.

Study PSC12

Study PSC12 was a Phase 3, observer-blinded, randomized, active controlled, relative efficacy trial conducted at 40 U.S. sites during the 2014-2015 influenza season. The

predominant influenza virus in circulation during this season in the U.S. was an A/H3N2 strain that was poorly matched to the A/H3N2 antigen present in the influenza vaccine formulations. The study was designed to evaluate the relative efficacy, immunogenicity and safety of Flublok Quadrivalent as compared to IIV4 in ambulatory, medically stable adults 50 years and older. A total of 8963 subjects were enrolled and randomized 1:1 to receive a single dose of Flublok Quadrivalent (180 mcg) or IIV4 (60 mcg) administered intramuscularly on study Day 0. Females and blacks/African Americans were somewhat overrepresented while Asians and Hispanics/Latinos were underrepresented relative to the U.S. population.

The primary endpoint of PSC12 was protocol-defined, reverse transcriptase polymerase chain reaction (rtPCR)-confirmed, influenza-like illness (ILI) beginning at least 14 days post-vaccination and caused by any influenza strain. To demonstrate non-inferior (NI) relative vaccine efficacy (rVE) of Flublok Quadrivalent as compared to IIV4, the success criteria for the primary endpoint was defined as:

- The lower bound of the two-sided 95% confidence interval (CI) of the rVE > -20%, where rVE = 1- Relative Risk (RR) = 1 - (Attack Rate $_{\text{FlublokQuadrivalent}}$ / Attack Rate $_{\text{IIV4}}$).

The population (efficacy population) used to analyze the rVE primary objective for study PSC12 comprised 8604 subjects and was defined as all randomized subjects who received study vaccine and provided any follow-up documentation for ILI beginning at least 14 days after vaccination. Subjects with significant protocol deviations that could adversely impact efficacy were excluded from the efficacy population. The data in Table 1 show that the success criterion for the primary endpoint was met.

Table 1: Relative Vaccine Efficacy of rtPCR-Confirmed ILI Due to All Influenza Virus Strains – PSC12 (Efficacy Population)

Flublok Quadrivalent N=4303	**Flublok Quadrivalent N=4303**	**IIV4 N=4301**	**IIV4 N=4301**	**Relative Risk (RR)**	**rVE (95% CI)**
N (# of cases)	Attack Rate (AR)	N (# of cases)	Attack Rate	$AR_{\text{Flublok Quadrivalent}}$ /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) = $AR_{\text{Flublok Quadrivalent}}$ / AR_{IIV4}
Relative Vaccine Efficacy (rVE) of Flublok Quadrivalent versus IIV4 = (1 – RR) x 100

The PSC12 protocol stated that rVE would be tested for superiority as an exploratory analysis if non-inferior rVE was demonstrated. Superior VE of Flublok Quadrivalent relative to IIV4 was pre-specified as a LB of the two-sided 95% CI of rVE > 9%. Though the success criterion of superiority was met (Table 1), the analysis of superiority was not pre-specified in the study's Statistical Analysis Plan and PSC was advised that a claim of superiority would not be included in the Flublok Quadrivalent package insert.

Post hoc, exploratory analyses of rVE according to influenza type A or B were performed by PSC but were not powered for statistical significance. The results 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).

Immunogenicity data were collected from 614 subjects (314 Flublok Quadrivalent and 300 IIV4 recipients) at 5 pre-selected study sites in PSC12. Flublok Quadrivalent immunogenicity as compared to IIV4 immunogenicity was evaluated as a secondary study endpoint. Serum was collected from subjects prior to vaccination (study Day 0) and 28 days following vaccination (study Day 28) to measure antibody seroconversion rates (SCRs) and geometric mean titers (GMTs). Seroconversion was defined as either a pre-vaccination hemagglutination inhibition (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 immunogenicity of the four Flublok Quadrivalent antigens was compared to the corresponding IIV4 antigens using Day 28 post-vaccination HI GMT ratios and SCR differences for a total of 8 secondary immunogenicity endpoints. The pre-specified success criteria for establishing the non-inferior immunogenicity of Flublok Quadrivalent as compared to IIV4 were as follows for all four vaccine antigens:

1. The upper bound of the 2-sided 95% confidence interval (CI) for the GMT ratio (GMT_{IIV4} / $GMT_{Flublok\ Quadrivalent}$) ≤ 1.5, *AND*
2. The upper bound of the 2-sided 95% confidence interval for the SCR difference ($SCR_{IIV4} - SCR_{Flublok\ Quadrivalent}$) ≤ 10%.

The study results showed that Flublok Quadrivalent met the GMT ratio success criterion for the A/H1N1, A/H3N2 and B/Yamagata antigens but failed to meet the GMT ratio success criterion for the B/Victoria antigen. The SCR success criterion was met for the A/H3N2 and B/Yamagata antigens but was not met for the A/H1N1 and B/Victoria antigens.

Study PSC16

Study PSC16 was a Phase 3, observer-blind, randomized, comparator-controlled trial conducted at ten U.S. sites during the 2014-2015 influenza season. The study was designed to evaluate the safety, reactogenicity, and immunogenicity of Flublok Quadrivalent compared to IIV4. The study was conducted in healthy, medically stable adults 18 to 49 years of age. A total of 1350 subjects were enrolled and randomized 3:1 to receive a single, 0.5 mL dose of Flublok Quadrivalent (180 mcg) or IIV4 (60 mcg) administered intramuscularly. The distribution of subject characteristics was generally balanced but males and Asians were underrepresented while females and Blacks/African Americans were overrepresented relative to the total U.S. population.

Serum was collected from subjects prior to vaccination (study Day 0) and 28 days following vaccination (study Day 28) to measure antibody SCRs and GMTs. Seroconversion was defined as for study PSC12.

The immunogenicity of the four Flublok Quadrivalent antigens were compared to the corresponding antigens in IIV4 using the CBER-defined criteria of Day 28 post-vaccination HI GMT ratios and SCR differences for a total of 8 co-primary endpoints. The pre-specified success criteria for establishing the non-inferior immunogenicity of Flublok Quadrivalent as compared to IIV4 were as follows for all four vaccine antigens:

1. The upper bound of the 2-sided 95% confidence interval (CI) for the GMT ratio (GMT_{IIV4} / $GMT_{Flublok\ Quadrivalent}$) ≤ 1.5, *AND*
2. The upper bound of the 2-sided 95% confidence interval for the SCR difference (SCR_{IIV4} − $SCR_{Flublok\ Quadrivalent}$) ≤ 10%.

The population (immunogenicity population) used to analyze the non-inferior immunogenicity primary objective for study PSC16 was defined as all randomized subjects who received a dose of study vaccine, provided serum samples for Day 0 and Day 28 HI antibody titers within specified windows, and subjects had no major protocol deviations that might adversely impact the immune response. The immunogenicity population comprised 1292 subjects of whom 969 received Flublok Quadrivalent and 323 received IIV4 (3:1 randomization). The results for SCRs, SCR differences, GMTs, GMT ratios and 95% CIs are shown in Tables 2 and 3.

Table 2: 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	Flublok Quadrivalent GMT (95% CI) N=969	IIV4 GMT (95% CI) N=323	GMT Ratio (95% CI)	Met GMT 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)	--	--
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; IIV4=Fluarix Quadrivalent; GMT=geometric mean titer.
*Success criteria for the GMT ratio (GMT_{IIV4} / $GMT_{Flublok\ Quadrivalent}$): UB of the 95% CI must be ≤ 1.5.

Table 3: 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	Flublok Quadrivalent SCR N=969 % (95% CI)	IIV4 SCR N=323 % (95% CI)	SCR Difference % (95% CI)	Met SCR Success 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; IIV4=Fluarix Quadrivalent; SCR=seroconversion rate.
*Success criteria for the SCR difference (SCR_{IIV4} - $SCR_{Flublok\ Quadrivalent}$): UB of the 95% CI must be ≤ 10%.

The data in Tables 2 and 3 show that the antibody response to Flublok Quadrivalent met the non-inferior success criteria for the GMT ratio and SCR difference co-primary endpoints for the A/H1N1, AH3/N2 and B/Yamagata vaccine antigens but failed to meet the success criteria for the B/Victoria antigen. Lower antibody responses to B-type as compared to A-type viruses are not uncommon and the low baseline antibody titers measured for the B antigens (Table 2, Day 0) suggest that the study population was immunologically naïve to the B-type (particularly B/Victoria) viruses which may have contributed to the low Day 28 titers. The use of whole, inactivated B-type viruses in place of the more typically used "split" B-type viruses in the HI assay used for PSC16 also likely contributed to the lower GMTs observed for the B versus the A antigens. The statistically significantly lower B/Victoria GMTs and SCRs observed for Flublok Quadrivalent recipients as compared to IIV4 recipients may also be due, in part, to antigenic differences between the B/Victoria rHA present in Flublok Quadrivalent and the egg-based B/Victoria antigen used in the HI assay. The sequence of the B/Brisbane rHA component in Flublok used in PSC12 and PSC16 differed from the egg-grown rHA at a glycosylation site, and therefore antigenic differences between rHA and egg-grown antigen used in the HI assay may result in lower antibody titers measured in sera from Flublok recipients as compared to recipients of the egg-grown, split vaccine IIV4 comparator. This is also suggested by ferret studies.

b) Pediatrics

Under STN 125285/0, PSC requested and was granted a waiver from studies of Flublok in children less than 3 years of age because data provided from a randomized, controlled study (PSC02) strongly suggested that Flublok would not be effective in children younger than 3 years of age. In this supplement (STN 125285/194) PSC also requested a waiver of studies of Flublok Quadrivalent in children less than 3 years of age. The waiver request was

presented to the FDA Pediatric Review Committee. Waiver of Flublok Quadrivalent studies in children less than 3 years was granted due to the similarity of composition and manufacturing process between Flublok and Flublok Quadrivalent.

Two postmarketing required pediatric studies were established in the January 16, 2013 approval letter for the original Flublok license application to fulfill the requirements of the Pediatric Research Equity Act (PREA). One study was in children 3-5 years old and the second study was in children 6-17 years old. In the Pediatric Study Plan included in this supplement, PSC proposed to conduct these studies using Flublok Quadrivalent. CBER agreed with PSC's plan which was presented to the FDA Pediatric Review Committee who also agreed that the proposal was acceptable. Subsequently, PSC proposed to combine the two PREA studies into a single, relative efficacy study (PSC17) in children 3-17 years of age. CBER agreed that the combined study could be used to fulfill the PREA requirements.

c) Bioresearch Monitoring

CBER Bioresearch Monitoring inspected two clinical study sites. Each site enrolled subjects for both study PSC12 and study PSC16. The inspections did not reveal significant problems that would impact the data submitted in the supplement.

d) Other Special Populations

Flublok has not been studied in pregnant/lactating women or immunocompromised individuals. During negotiations preceding the January 16, 2013 approval of the original Flublok license application, PSC agreed to establish a prospective pregnancy registry to monitor pregnant women immunized with Flublok. This commitment remains to be completed and PSC plans to revise the protocol for this study (PSC15) to include Flublok Quadrivalent recipients.

7. Safety

The safety population for studies PSC12 and PSC16 comprised 10,002 subjects and was defined as all subjects who received a dose of study vaccine and for whom any safety data (PSC16) or any evaluable safety data (PSC12) were available after vaccination. There were 1330 subjects (of whom 998 received Flublok Quadrivalent) from study PSC16 (18-49 years) and 8672 subjects (of whom 4328 received Flublok Quadrivalent) from study PSC12 (≥50 years), for a total of 5326 subjects who received a single 180 mcg dose of Flublok Quadrivalent and 4676 subjects who received a single 60 mcg dose of IIV4. The safety population was used for the analyses of unsolicited adverse events (AEs), serious adverse events (SAEs), and medically attended adverse events (MAEs). Among all subjects, 13.3% were 18-49 years, 51.8% 50-64 years, and 34.8% ≥65 years. To evaluate safety, both studies actively solicited local and systemic reactogenicity events for 7 days, collected unsolicited AEs for 28 days, and collected both SAEs and MAEs for 6 months post-vaccination. Safety was summarized using descriptive statistics. Overall, the safety of Flublok Quadrivalent was acceptable and comparable to IIV4 in adults ≥18 years of age.

Deaths and Discontinuations

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.

SAEs and MAEs

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 none appeared clearly related to study vaccines. Other than an imbalance of ILIs (more in IIV4 recipients), MAEs were balanced between treatment groups.

Adverse Events of Special Interest (AESIs)

During the six months post-vaccination, no subjects 18-49 years (PSC16) or ≥50 years (PSC12) experienced AESIs (potential risks associated with influenza vaccines and defined in the sponsor's pharmacovigilance plan), 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.

Solicited Local and Systemic AEs

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 Quadrivalent 47.9%, IIV4 46.7%) and pain (Flublok Quadrivalent 36.8%, IIV4 36.4%). The rates of injection site redness were low but occurred more frequently among Flublok Quadrivalent recipients as compared to IIV4 (4.2% versus 0.9%). The most common systemic symptoms were headache (Flublok Quadrivalent 20.3%, IIV4 21.1%), fatigue (Flublok Quadrivalent 16.5%, IIV4 16.6%),

muscle pain (Flublok Quadrivalent 12.8, IIV4 11.7%), and joint pain (Flublok Quadrivalent 9.5%, IIV4 10.2%). Among adults ≥50 years, the most common local reactogenicity events were injection site tenderness (Flublok Quadrivalent 34.3%, IIV4 37.1%) and pain (Flublok Quadrivalent 18.9%, IIV4 22.0%). The most common solicited systemic symptoms were headache (Flublok Quadrivalent 12.7%, IIV4 13.5%), fatigue (Flublok Quadrivalent 12.2%, IIV4 12.2%), muscle pain (Flublok Quadrivalent 8.5%, IIV4 8.8%), and joint pain (Flublok Quadrivalent 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.

Postmarketing AEs

CBER review of the Vaccine Adverse Event Reporting System (VAERS) identified anaphylaxis and other severe allergic reactions after Flublok trivalent vaccine, particularly among individuals with a self-reported history of egg allergy or allergy to influenza vaccines. No deaths have been reported and no safety signals have been identified, but many of the reports describe life-threatening reactions that necessitated emergency treatment. Some patients experienced persistent wheezing and swelling—even after receiving epinephrine, nebulizers, and antihistamines. Thus far there are no reports of positive rechallenge, i.e., similar reaction after subsequent doses of Flublok.

VAERS is a passive surveillance system with potential for reporting bias and is lacking in denominator data. The number and variety of cases reported for Flublok did not allow for conclusions regarding a causal relationship or for an estimate of relative risk.

8. Advisory Committee Meeting

A Vaccines and Related Biologics Products Advisory Committee (VRBPAC) meeting was not held for this supplement. A VRBPAC meeting was held on November 19, 2009, for the original Flublok licensing application (STN 125285/0) and there were no issues associated with this supplement that required a new Advisory Committee meeting.

9. Other Relevant Regulatory Issues

PSC committed to establishing a pregnancy registry (study PSC15) for Flublok under the original Flublok licensure application (STN 125285/0). PSC stated that the protocol for PSC15 will be revised to include Flublok Quadrivalent recipients. PSC also committed to conducting an observational Phase 4 safety study (PSC13) under STN 125285/0. This study will include recipients of Flublok but not Flublok Quadrivalent. If PSC13, postmarketing safety surveillance, or other sources of data suggest a signal of serious risk or potential for serious risk, then the CBER Office of Biostatistics and Epidemiology, Division of Epidemiology may recommend a phase 4 study to evaluate the safety of Flublok Quadrivalent.

10. Labeling

In addition to the Flublok Quadrivalent package insert (PI), a revised Flublok (trivalent) PI was also provided because the relative vaccine efficacy data from PSC12 was used to support traditional approval of Flublok in persons 50 years and older as well as approval of Flublok

Quadrivalent in this population. The Flublok Quadrivalent package insert (PI) included safety and efficacy data from studies PSC12 and PSC16. The Flublok PI was revised to include efficacy data from PSC12. To comply with the 2014 draft FDA Guidance for Industry, "*Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format*" significant revisions were made to Section 8, *Use in Specific Populations*, of both PIs. The PIs were primarily reviewed by the Clinical, Pharmacovigilance and Advertising and Promotional Labeling Branch Reviewers.

Due to continuing postmarketing VAERS reports of anaphylaxis-like reactions in Flublok recipients with known allergies (including to eggs) or reactions to previous influenza vaccinations, the Pharmacovigilance and Clinical Reviewers recommended revising a portion of Section 6.2, *Post-marketing Experience*, of the Flublok Quadrivalent package insert from:

> *Immune system disorders: anaphylaxis, anaphylactoid reactions, allergic reactions, and other forms of hypersensitivity.*
>
> to:
>
> *Immune system disorders: anaphylaxis, anaphylactoid reactions, allergic reactions, and other forms of hypersensitivity including reactions among people with a self-reported history of egg allergy or previous allergic reaction to influenza vaccine.*

The rationale for the revision was to clarify that the risk of anaphylaxis and other hypersensitivity reactions following influenza vaccination is not necessarily related to egg proteins, and might help providers and patients to make a more informed decision regarding the use Flublok or Flublok Quadrivalent. The proposed revision was discussed by management within the CBER Office of Vaccines Research and Review (OVRR) who considered the presentation of post-marketing reports of anaphylaxis and other allergic reactions in the current approved Flublok (trivalent) package insert to be appropriate, sufficient, and consistent with this section of labeling for other vaccines. OVRR did not concur with the proposed qualification so it was not included in the PI.

All other labeling issues (including those for carton and container labeling) were satisfactorily resolved through communication with PSC.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The safety, efficacy and immunogenicity data provided in this supplement support the use of Flublok Quadrivalent for the prevention of influenza disease caused by influenza virus subtypes A and types B contained in the vaccine. The review committee recommends traditional approval of Flublok Quadrivalent in persons 18 years of age and older. The data provided also confirm the clinical benefit of Flublok (trivalent

formulation) and the review committee recommends traditional approval of Flublok in persons 50 years and older.

b) Risk/Benefit Assessment

Overall, the safety of Flublok Quadrivalent was acceptable and comparable to IIV4 in adults ≥18 years of age and no safety signals were identified. In persons ≥ 50 years, Flublok Quadrivalent demonstrated greater vaccine efficacy relative to a U.S.-licensed quadrivalent influenza vaccine (IIV4, Fluarix Quadrivalent) during a season in which an antigenically mismatched influenza A/H3N2 predominated. Flublok Quadrivalent also demonstrated non-inferior immunogenicity in persons 18-49 years as compared to IIV4 against 3 of the 4 antigens present in the vaccine. Non-inferior immunogenicity against the B/Victoria antigen was not demonstrated in this population. Thus, effectiveness of Flublok Quadrivalent 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. However, the lower B/Brisbane antibody titers elicited by Flublok Quadrivalent as compared to those elicited by IIV4 may be due to antigenic differences between the B/Brisbane rHA and the egg-grown B/Brisbane antigen used in the HI assay. 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 in any particular year.

Potential advantages of Flublok Quadrivalent relative to egg-based influenza vaccines include closer antigenic matching to circulating strains due to recombinant technology which preserves the protein sequence of the HA antigen 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. Regarding the potential advantages of Flublok Quadrivalent in persons with egg allergy, an increasing body of published evidence and recommendations from the Advisory Committee on Immunization Practices (ACIP) 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 the absence of egg proteins in Flublok Quadrivalent may not confer significant additional benefit over egg-based influenza vaccines in most persons with egg allergy.

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

c) Recommendation for Postmarketing Risk Management Activities

There were no recommendations for a Risk Evaluation and Mitigation Strategy (REMS) or a Postmarketing Requirement.

d) Recommendation for Postmarketing Activities

The relative vaccine efficacy study (PSC17) of Flublok Quadrivalent in children 3-17 years is a deferred study required by the Pediatric Research Equity Act. An agreement was reached with PSC on the general plan and timing of this study.