Summary Basis for Regulatory Action

Date: October 28, 2014

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

BLA/ STN#: 125285/78

Applicant Name: Protein Sciences Corporation

Date of Submission: October 21, 2013

PDUFA Goal Date: October 29, 2014

Proprietary Name/ Established Name: Flublok, Influenza Vaccine

Indication: Prevention of influenza disease in persons 50 years of age and older caused by influenza virus subtypes A and type B contained in the vaccine.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, 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 – 23 October 2014
Statistical Review	Barbara Krasnicka, PhD – 27 October 2014
Pharmacovigilance Review	Emily Jane Woo, MD, MPH – 08 October 2014
CMC Review	Maryna Eichelberger, PhD – 09 March 2014
Bioresearch Monitoring Review	Anthony Hawkins – 30 July 2014
Labeling Review	Sonny Saini – 07 July 2014, 18 September 2014, 20 October 2014 Cynthia Nolletti, MD – 20 October 2014 Emily Jane Woo, MD, MPH – 20 October 2014

1. Introduction

Flublok® is a trivalent vaccine manufactured by Protein Sciences Corporation (PSC) for the active immunization of persons 18 through 49 years of age for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. It is an influenza vaccine formulated as a sterile, aqueous, buffered solution of purified, recombinant influenza hemagglutinins (rHAs) and contains no egg proteins. The three rHAs are produced in *Spodoptera frugiperda* insect cells using a Baculovirus Expression Vector System (BEVS) in which the insect cells are infected with a baculovirus engineered to contain the gene for the corresponding influenza HA antigen. Each 0.5 mL dose of Flublok contains 135 mcg of rHA antigens (45 mcg each of H1, H3 and B rHAs) and may contain residual amounts (≤ 28.5 mcg) of baculovirus and insect cell proteins.

PSC submitted supplement STN 125285/78 on October 21, 2013, to expand the Flublok indication for the prevention of influenza disease to persons 50 years of age and older based on safety and immunogenicity data from three studies conducted in the U.S. Studies PSC03 and PSC06 were Phase 3 immunogenicity and safety studies conducted in adults 50 through 64 years of age and 65 years of age and older, respectively. Study PSC11 was a Phase 3/4 clinical safety study conducted in persons 50 years of age and older. Revised Flublok labeling was also provided with the supplement.

2. Background

Flublok was licensed in the United States for persons 18-49 years of age on January 16, 2013. Efficacy, immunogenicity and safety data from two clinical studies (PSC03 and PSC06) in persons 50 years and older were included in the original license application. Members of a Vaccines and Related Biological Products Advisory Committee (VRBPAC) that met on November 19, 2009, to discuss the safety and efficacy of Flublok in persons 18 years and older, expressed concerns regarding the relatively small size of the Flublok safety database in all age groups, particularly in persons 50 years of age and older. Though no clear safety signals were identified in the pivotal study (PSC04) supporting the original Flublok license application (STN 125285/0), a small imbalance in possible hypersensitivity events was observed. Thus, PSC agreed to conduct study PSC11 to collect additional safety data, including hypersensitivity events, in persons 50 years of age and older. CBER agreed that study PSC11, together with studies PSC03 and PSC06, could be submitted for consideration in support of Flublok licensure in this age group. Because influenza vaccines generally are less effective in older persons and because Flublok is a non-egg based influenza vaccine with a less well-established relationship between immune response and efficacy as compared to egg-based influenza vaccines, CBER also reached an agreement with PSC that approval based on data from PSC03, PSC06 and PSC11, if granted, would be under accelerated approval regulations and that PSC would be required to conduct a confirmatory clinical efficacy trial in persons 50 years of age and older. As part of the January 16, 2013 licensure, PSC also agreed to conduct an observational, Phase 4 study in persons 18-49 years old to further expand Flublok's safety database.

The hemagglutination inhibition (HI) assay was used in studies PSC03 and PSC06 to measure antibody titers and, thus, to evaluate whether the immunogenicity of Flublok was non-inferior to that of two U.S.-licensed influenza vaccines. This assay is used to calculate seroconversion rates (SCRs), defined as the percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥1:40 or a pre-vaccination HI titer ≥1:10 and a minimum four-fold rise in post-vaccination HI antibody titer. The assay is also used to calculate SCR differences (the difference between Flublok and comparator SCRs) and geometric mean titer (GMT) ratios (the ratio of comparator GMTs to Flublok GMTs). CBER agreed that PSC could use rHA antigens in place of the traditionally used egg-derived influenza antigens in the HI assay. A comparison of results of the HI assay using egg-derived antigens versus results of the assay using rHAs was submitted in the original Flublok application. The comparison showed that antibody titers assessed by the HI assay using rHA antigens were consistently higher than titers determined using egg-derived influenza antigens in the assay. This finding is likely due to the smaller size and fewer antibody binding sites on the surface of antigens formed by the Flublok rHAs compared to antigens in egg-derived, inactivated influenza vaccines. Thus, interpretation of the proportion of subjects whose post-vaccination HI antibody titer exceeds 1:40 is less certain when rHAs are used in the HI assay. The interpretation of SCRs and SCR differences are similarly uncertain. In contrast, GMT ratios may be mathematically less likely to be affected by using rHAs in the HI assay. For this reason, CBER informed PSC that only GMT ratio data from studies PSC03 and PSC06 would be considered in support of demonstrating the effectiveness of Flublok compared to a U.S.-licensed influenza vaccine.

PSC submitted STN 125285/78 on October 31, 2013. CBER issued a Refuse to File (RTF) letter on December 13, 2013, because the supplement was incomplete and inadequately organized. PSC requested a meeting which was scheduled for January 22, 2014, during which CBER advised PSC on how to correct the deficiencies. PSC provided a revised supplement (Amendment 8) on February 18, 2014, and requested that it be filed over protest (FOP). CBER issued a FOP acknowledgment letter to PSC on March 6, 2014 stating that the supplement had been filed on February 18, 2014, with a new action date of October 29, 2014.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

No manufacturing changes were made and no manufacturing information was submitted in support of this supplement.

b) CBER Lot Release

There are no pending lots or issues that would preclude approval of this supplement.

c) Facilities Review/Inspection

There are no ongoing or pending investigations or compliance actions with respect to PSC's facilities or products. There are also no ongoing or pending investigations or compliance actions

with respect to PSC's contracting facility. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management did not object to approval of this supplement.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted in support of this supplement.

5. Clinical Pharmacology

No new clinical pharmacology data were submitted in support of this supplement.

6. Clinical/ Statistical

a) Clinical and Statistical Summary of Immunogenicity Results

The immunogenicity of Flublok was evaluated in a total of 1462 persons aged 50 years and older in two clinical studies, PSC03 and PSC06. Of these subjects, 730 received Flublok and 732 received a U.S.-licensed, trivalent inactivated influenza vaccine (IIV3), Fluzone. There were 601 subjects aged 50 through 64 years and 861 subjects were 65 years of age or older.

Study PSC03

Study PSC03 was a Phase 3, prospective, randomized, modified double-blind, comparator-controlled trial conducted at six U.S. sites during the 2006-2007 influenza season. The study was designed to evaluate the immunogenicity, safety and reactogenicity of Flublok as compared to IIV3 in ambulatory, medically stable adults age 65 and older. A total of 870 subjects enrolled were randomized 1:1 to receive a single dose of Flublok (135µg) or IIV3 (45µg) administered intramuscularly on study Day 0. The study population was comprised primarily of Caucasian subjects with under-representation of African-Americans, Hispanics, and Asians relative to the general U.S. population.

Two co-primary endpoints were pre-specified for each of the three vaccine virus strains:

1. GMT ratios at study Day 28; *AND*
2. SCR differences at study Day 28.

To demonstrate non-inferiority (NI) of the immunogenicity of Flublok as compared to IIV3, the success criteria for the co-primary endpoints above were defined as:

1. The upper bound (UB) of the two-sided 95% confidence interval (CI) for the GMT ratio (GMT IIV3 / GMT Flublok) must be ≤ 1.5; *AND*
2. The UB of the two-sided 95% CI for the difference in SCRs (SCR IIV3 – SCR Flublok) must be ≤ 10%.

The Evaluable Population for PSC03, was defined as those subjects with available study Day 28 immunogenicity data, comprised 861 subjects, 431 of whom received Flublok and 430 of whom received IIV3. As explained above (Section 2, *Background*), only GMT ratios were considered by CBER in support of demonstrating the effectiveness of Flublok compared to IIV3. GMT titers, GMT ratios and 95% CIs results from PSC03 are shown in Table 1. The results demonstrate that the success criterion for the GMT co-primary endpoint for PSC03 was met.

Table 1. PSC03 Study Day 28 GMTs, GMT ratios and CIs*

Antigen	**Day 28 GMT IIV3**	**Day 28 GMT Flublok**	**GMT ratio (GMT IIV3/GMT Flublok)**	**95% CI of GMT ratio**	**Success criterion met?**
H1	148.1	176.8	0.84	(0.81, 0.86)	Yes
H3	199.2	338.5	0.59	(0.57, 0.60)	Yes
B	194.8	149.6	1.30	(1.26, 1.34)	Yes

*Source: STN 125285/78.8, Module 5, PSC03 CSR, Tables 15 and 14.2.1.1.

The success criterion for the SCR difference co-primary endpoint was met for the H1 and H3 antigens but not for the B antigen because the UB of the 95% CI was 16.1%.

Secondary endpoints and success criteria were also pre-specified for each treatment group. The secondary endpoints were the proportion of subjects in each treatment group with post-vaccination HI titers of ≥ 1:40 at study Day 28 for each of the three vaccine virus strains. Both Flublok and IIV3 met the success criteria that the lower bound (LB) of the two-sided 95% CI must be ≥ 60% for each of these three endpoints.

<u>Study PSC06</u>

Study PSC06 was a Phase 3, prospective, randomized, modified double-blind, comparator-controlled trial conducted at six U.S. sites during the 2007-2008 influenza season. The study was designed to evaluate the immunogenicity, safety and reactogenicity of Flublok versus IIV3 in healthy adults 50 through 64 years of age. A total of 602 subjects were enrolled and randomized 1:1 to receive a single dose of Flublok (135µg) or IIV3 (45µg) administered intramuscularly on study Day 0. The study population was balanced between the treatment arms with under-representation of Caucasian and African-American subjects and over-representation of Asian subjects relative to the general U.S. population.

Two co-primary endpoints and success criteria were defined for each of the three vaccine virus antigens. The first co-primary endpoint was the SCR at study Day 28, and the success criterion was that the lower bound (LB) of the 2-sided, 95% CI must be ≥ 40%. The second co-primary endpoint was the proportion of subjects with a post vaccination HI antibody titer of ≥ 1:40 at study Day 28, and the success criterion was that the LB of the 95% CI must be ≥ 70%. The study met the success criteria for all three antigens for the second co-primary endpoint. The study met the success criteria for the H1 and H3 antigens but missed the success criterion for the B antigen because the LB of the 95% CI was 35.2%.

Study PSC06 pre-specified an analysis of GMT ratios as one of two co-secondary endpoints for each of the three vaccine antigens. The co-secondary endpoints were:

1. GMT ratio (GMT IIV3 / GMT Flublok) at study Day 28 *AND*,
2. SCR difference (SCR IIV3 – SCR Flublok) at study Day 28

The success criteria to be met to demonstrate non-inferior immunogenicity of Flublok as compared to IIV3 were defined as:

1. The upper bound (UB) of the two-sided 95% CI for the GMT ratio must be ≤ 1.5 *AND*,
2. The UB of the two-sided 95% CI for the SCR difference must be ≤ 10%.

The evaluable population for study PSC06 comprised 601 subjects of whom 299 received Flublok and 302 received IIV3. The results for GMTs, GMT ratios and 95% CIs shown in Table 2 demonstrate that Flublok met the GMT ratio success criterion for each of the three vaccine strains.

Table 2. PSC06 Study Day 28 GMTs, GMT ratios and CIs*

Antigen	**Day 28 GMT IIV3**	**Day 28 GMT Flublok**	**GMT ratio (GMT IIV3 / GMT Flublok)**	**95% CI of GMT ratio**	**Success criterion met?**
H1	139.74	181.34	0.77	(0.75, 0.79)	Yes
H3	60.88	105.41	0.58	(0.53, 0.62)	Yes
B	116.03	110.93	1.05	(1.01, 1.09)	Yes

*Source: STN 125285/78.8, Module 5, PSC06 CSR, Tables 7 and 14.2.2.1.

b) Bioresearch Monitoring Review

CBER Bioresearch Monitoring inspected four clinical sites from study PSC11 for this application. The inspections did not reveal significant problems that would impact the data submitted in the supplement.

c) Pediatric Research Equity Act (PREA)

The Pediatric Research Equity Act does not apply to this supplement because it was not submitted in support of a new indication, new dosage form, new dosing regimen or new route of administration and Flublok was not formulated to contain a new active ingredient. Two postmarketing required pediatric studies in persons 3 through 17 years of age were specified in the January 16, 2013 approval letter for the original Flublok license application, STN 125285/0 and are pending completion. PSC was waived from studies of Flublok in children less than 3 years of age because data from a randomized, controlled study strongly suggested that Flublok would not be effective in children younger than 3 years of age.

d) Other Special Populations

Flublok has not been studied in pregnant/lactating women or immunocompromised individuals. For 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.

7. Safety

Both safety and immunogenicity data were collected in studies PSC03 and PSC06. A third study, PSC11, was designed to expand the safety database in persons 50 years and older. The safety population for studies PSC03, PSC06 and PSC11 included 4098 of the 4112 persons enrolled. Flublok was administered to 2050 subjects (972 were 50 through 64 years old and 1078 were 65 years of age or older) and 2048 subjects received IIV3 (967 were 50 through 64 years old and 1081 were 65 years of age or older). Thirteen of the 14 subjects for whom safety data were not provided were from PSC11. Eleven of these subjects were lost to follow-up. One subject from PSC03 was randomized but not vaccinated. No subject dropped out or was discontinued due to adverse events (AEs).

Safety endpoints common to all three studies included the proportions of subjects in each treatment group reporting solicited local (injection site pain, erythema/redness, and firmness/swelling) or systemic (fever, chills/shivering, fatigue/lack of energy/malaise, myalgia, arthralgia, headache, and nausea) reactogenicity events in the 7 days post-vaccination, unsolicited AEs occurring within 28 to 30 days post-vaccination and serious adverse events (SAEs) occurring within 30 days (PSC11) or 180 days (PSC03 and PSC06) post-vaccination.

Study PSC11

Study PSC11 was a Phase 3/4 prospective, randomized, observer-blind, comparator-controlled trial conducted at 14 U.S. sites during the 2012-2013 influenza season. It was designed to evaluate the safety and reactogenicity of Flublok as compared to a U.S.-licensed IIV3 (Afluria) in ambulatory, medically stable adults 50 years of age and older. A total of 2640 subjects were enrolled and stratified into 2 approximately equal age groups, 50-64 years and ≥65 years, and randomized 1:1 to receive either 135mcg of Flublok (1319 subjects) or 45mcg of IIV3 (1321 subjects) administered intramuscularly as a single dose. Females and Caucasians were over-represented in the study population as compared to the broader U.S. population, primarily in the 50-64 year old age group.

The primary endpoint of PSC11 was a pre-specified composite of the proportion of subjects from study Day 0 through Day 30 reporting common, systemic, hypersensitivity-type adverse events categorized as:

- Rash
- Urticaria
- Swelling
- Non-dependent edema

- Other: Unsolicited AEs suggestive of hypersensitivity reactions evaluated for inclusion prior to database lock and study unblinding

The success criterion to be met to demonstrate safety non-inferiority of Flublok as compared to IIV3 was that the UB of the one-sided 97.5% CI of the difference in the rates of hypersensitivity AEs between Flublok and IIV3 must be < 1.5%.

A larger proportion of Flublok recipients reported hypersensitivity type events in the 30 days following vaccination as compared to IIV3 (2.4% versus 1.6%, respectively) with an UB of 1.91% for the 97.5% CI around the rate difference. Thus, the non-inferiority criterion for the primary endpoint was not met. The hypersensitivity imbalance was also observed in the first 7 days post-vaccination (1.9% vs 0.9%), a time period more relevant for immediate or IgE-mediated hypersensitivity and possibly more suggestive of causality.

PSC defined a post-hoc, exploratory endpoint of "adjudicated hypersensitivity events" because more than 82% of subjects reporting hypersensitivity events did not return to the study site within 24 hours of event onset for evaluation as specified in the clinical protocol. The success criterion for the exploratory endpoint was the same as that for the pre-specified primary endpoint. All of the 52 subject-reported hypersensitivity events were adjudicated by two blinded, external, expert reviewers (one of whom had expertise in allergy/immunology and the other in dermatology) to create a list of 10 events that were thought to be Type 1, IgE-mediated hypersensitivity events. The post-hoc, adjudicated endpoint did meet PSC's success criterion.

Safety Summary: PSC03, PSC06 and PSC11

Solicited Local and Systemic AEs

Overall, the results from studies PSC03, PSC06 and PSC11 indicate that the reactogenicity profile for Flublok is comparable to other IIV3s. No large imbalances in the rates or intensities of solicited AEs between Flublok and IIV3 comparators were observed in either age group. AEs were generally mild to moderate. Solicited AEs reported by ≥10% of Flublok recipients 50-64 years of age included injection site pain, headache, fatigue, and muscle pain. Solicited AEs reported by ≥10% of Flublok recipients 65 years of age and older were injection site pain, fatigue, and headache. Severe reactions were uncommon ranging from 0.5% in PSC11 to 3% in PSC06 and were generally balanced in frequency between the two treatment groups. Severe, systemic AEs were reported in more Flublok as compared to IIV3 recipients (1.2% versus 0.6%, respectively) in PSC11, however, no large imbalance was noted between treatment groups for any single systemic AE. The frequencies of reactogenicity events in adults ≥65 years of age were generally lower than in adults 50-64 years of age.

As noted earlier, a greater proportion of Flublok recipients reported hypersensitivity-type events as compared to IIV3 recipients in study PSC11. Rash was the most frequently reported event in both Flublok and IIV3 groups in this study. Two severe hypersensitivity-type events (rash and urticaria) were reported by Flublok recipients in PSC11but these were assessed as unrelated to vaccine. Following adjudication of the hypersensitivity-type events by experts, no imbalance was observed. There were no reports of anaphylaxis across the three studies.

Unsolicited AEs

Unsolicited AEs were reported much less frequently than solicited AEs. They were generally of mild to moderate intensity and of similar proportions between Flublok and IIV3 recipients. Injection site reactions were the most common, unsolicited AEs assessed as related to vaccination and were generally balanced between treatment groups though a slightly higher percentage of Flublok as compared to IIV3 recipients in PSC03 reported such events (4% versus 2%, respectively). Only three unsolicited AEs assessed as severe in intensity appeared related to Flublok: injection site swelling (PSC03), rash, and fatigue (PSC11). All resolved without sequelae. No unusual patterns or trends in unsolicited AEs were noted. No imbalances in hypersensitivity events were identified in studies PSC03 and PSC06. One subject, a 52 year old female Flublok recipient experienced mild urticaria 4 days following vaccination which was assessed as possibly related to the study vaccine. The event resolved without sequelae after treatment with medication.

SAEs and deaths

SAEs (including 4 deaths) occurred in 2.1% and 2.3% of Flublok and IIV3 recipients, respectively, across the three studies (through Day 180 for PSC03 and PSC06; through Day 30 for PSC11). The types of SAEs were similar between treatment groups and no Flublok recipients were discontinued due to AEs. Only 1 SAE across all three studies, a case of vasovagal syncope following vaccination of a 57 year old male in PSC03, was considered as attributable to Flublok and is a well-described complication following intramuscular injection.

No vaccine-related deaths occurred in any of the studies. Two deaths occurred in Flublok recipients in study PSC03. One 89 year old female with hypertension died of a pontine hemorrhage-b(6)- months following vaccination and an 80 year old female with diverticulosis developed bowel perforation and secondary peritonitis/sepsis 4 days following vaccination. The subject declined intubation for respiratory distress following bowel resection and died b(6) days following vaccination. Two deaths also occurred in IIV3 recipients in PSC03. No deaths were reported in PSC06 or PSC11.

Postmarketing AEs

The Vaccine Adverse Event Reporting System (VAERS) received 12 reports between the initial date of Flublok licensure (January 16, 2013) and July 31, 2014, describing signs and symptoms consistent with acute hypersensitivity reactions after Flublok administration. All 12 occurred within 2 days of receiving Flublok. Nine of the 12 reports were considered to be possible anaphylaxis due to the rapidity and severity of symptoms. All patients were females and most were 40-50 years old with a history of allergies (particularly to eggs) or previous reactions to other influenza vaccines. No fatalities or hospitalizations were reported, although one patient was held in the emergency department for overnight observation. In all cases, Flublok was listed as the only vaccine, i.e., there were no concomitant immunizations as a potential cause of the events.

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

There were no other relevant regulatory issues associated with this supplement.

10. Labeling

The Flublok package insert (PI) was revised to include the safety and immunogenicity data from studies PSC03, PSC06 and PSC11. The PI was reviewed primarily by the Clinical, Pharmacovigilance and Advertising and Promotional Labeling Branch Reviewers. An updated Patient Information Sheet was also submitted but was withdrawn from the supplement on October 10, 2014, after PSC decided not to distribute this sheet for the remainder of the 2014/2015 influenza season following approval of this supplement. A "Dear Healthcare Provider" letter was submitted (Amendment 15) and was also withdrawn after PSC was informed on September 5, 2014, that such letters should not be used only as an announcement of a new indication or expansion of an existing indication to a new population.

While the small imbalances in hypersensitivity events noted above for PSC11 and PSC04 were not clinically important, the postmarketing VAERS reports of anaphylaxis-like reactions in subjects with known allergies or reactions to previous vaccinations prompted an internal discussion during which it was agreed that the available data, including the VAERS reports, did not allow for attribution of the reactions specifically to any particular component of the vaccine, such as insect cell proteins. However, the clinical review team recommended the addition of a more explicit description of the postmarketing VAERS reports to the Highlights section and the pharmacovigilance reviewer proposed revisions to the *Warnings and Precautions* sections of the package insert. OVRR IOD decided that a reference to section 6.2, *Postmarketing Experience*, in the *Contraindications* section of the Highlights would be sufficient to draw attention to the information in the VAERS reports. PSC agreed with this recommendation. All other labeling issues were satisfactorily resolved through communication with PSC.

The Flublok carton and container labels were appropriately revised for the expansion of the indication to persons 50 years and older.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The safety and immunogenicity data provided in this supplement support the expansion of the Flublok indication for the prevention of influenza disease caused by influenza virus

subtypes A and type B contained in the vaccine to persons 50 years of age and older. The review committee recommends approval of this supplement.

b) Risk/Benefit Assessment

Immunogenicity data (GMT ratios) from studies PSC03 and PSC06 support effectiveness of Flublok in persons 50 years and older as compared to a U.S.-licensed, influenza vaccine. The most common risks associated with Flublok (and also with IIV3) in this age group were injection site pain, headache and fatigue. The events were mostly mild and resolved within several days. The interpretation of a small imbalance in self-reported, hypersensitivity-type adverse events observed in study PSC11 is limited by the failure of most of the subjects (>82%) to return to the study site within 24 hours of event onset for follow-up. The imbalance was not observed following adjudication of the events by experts. The interpretation of VAERS reports of anaphylaxis in Flublok recipients is limited by the small number of cases and other confounding factors.

c) Recommendation for Postmarketing Risk Management Activities

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

d) Recommendation for Postmarketing Activities

An internal discussion was held to determine whether the VAERS hypersensitivity-type reports discussed above (Section 7, *Safety*) would require a postmarketing study. It was decided that FDA's Mini-Sentinel system would be better suited to evaluate hypersensitivity reactions in Flublok recipients.

Approval of this supplement will be based on accelerated approval regulations. Thus, a postmarketing requirement (PMR) will be to conduct a confirmatory efficacy study in persons 50 years and older. Additionally, PSC will be released from the Phase 4 postmarketing commitment (PMC) established under the original Flublok approval (STN 125285/0) and that commitment will be re-established under this supplement (item #2 below) to include the expanded population. An agreement was reached with PSC on the general plan and timing of these studies.

The following postmarketing activities are included in the approval letter:

Accelerated Approval Required Study subject to 21CFR 601.70 reporting requirements

1. To conduct a confirmatory clinical efficacy and safety study (PSC12) in adults 50 years of age and older for active immunization for the prevention of disease caused by influenza virus subtypes A and types B contained in your investigational quadrivalent influenza vaccine manufactured according to the same process as Flublok.

   Final Protocol Submission: October 21, 2014

Study/Trial Completion: June 30, 2016

Final Report Submission: June 30, 2017

Agreed Upon Postmarketing Commitments subject to 21CFR 601.70 reporting requirements

2. To conduct an observational postmarketing safety study (PSC13) in approximately 25,000 Flublok recipients 18 years of age and older to further characterize the safety profile of Flublok using recipients of U.S.-licensed, egg-based, trivalent or quadrivalent inactivated influenza virus vaccines as a comparator, with appropriate adjustment or matching for important covariates such as sex and age.

   Final protocol submission date: April 30, 2015

   Study/trial completion date: June 30, 2017

   Final Report Submission date: June 30, 2018