# Summary Basis for Regulatory Action

**Date:** January 16, 2013

**From:** Timothy Fritz, Ph.D., Committee Chair

**BLA/ STN#:** 125285/0

**Applicant Name:** Protein Sciences Corporation

**Date of Original Submission:** April 18, 2008

**PDUFA Goal Date:** January 16, 2013 (for the July 17, 2012 resubmission)

**Proprietary Name:** Flublok

**Established Name:** Influenza Vaccine

**Indication:** Flublok is indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B represented in the vaccine. Flublok is approved for use in persons 18 to 49 years of age.

**Dosage Forms:** Suspension for injection supplied in 0.5 mL single-dose, pre-filled vials.

**Recommended Action:** Approval

**Signatory Authorities Action:** Approval

**Office Signatory Authority:** Marion Gruber, Ph.D., Director, 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.**

**Office Signatory Authority:** Mary Malarkey, Director, Office of Compliance and Biologics Quality

☐ **I concur with the summary review.**
☐ **I concur with the summary review and include a separate review to add further analysis.**
☐ **I do not concur with the summary review and include a separate review.**

| **Specific documentation used in developing the SBRA** | **Reviewer Name –Date of Review** |
|---|---|
| Clinical Review | Cynthia Nolletti, M.D.- 16 January, 2013 |
| Pharmacovigilance Review | Patricia Rohan, M.D.- 14 December, 2009<br>Jane Woo, M.D.- 11 December, 2012 |
| Statistical Review, Clinical | Barbara Krasnicka, Ph.D.- 28 November, 2012 |
| Statistical Review, Bioassay | Lev Sirota, Ph.D.- 21 September, 2009 |
| Product Review | Arifa Khan, Ph.D.- 15 January, 2013<br>Maryna Eichelberger, Ph.D.- 21 January, 2010 and 15 January, 2013<br>Matthew Sandbulte, Ph.D.- 25 January, 2010 |
| Testing Method and Analytical Chemistry | Maryna Eichelberger, Ph.D.- 15 January, 2013<br>Karen Campbell- 11 January, 2013<br>Manju Joshi- 10 September, 2010, 12 March 2012 and 21 December, 2012 |
| Developmental Toxicology Review | Marion Gruber, Ph.D.- 28 September, 2009 |
| Bioresearch Monitoring Review | Robert Wesley – 28 August, 2008 |
| Facilities and Establishment Inspection Report | Deborah Trout- 01 September, 2009, 01 October, 2010 and 10 January, 2013 |
| Proprietary Name | Jean Makie- 26 August, 2009<br>Maryann Gallagher- 10, October 2012 |
| Labeling Reviews | Maryann Gallagher- 24 September, 2012<br>Jean Makie- 23 October, 2009<br>Daphne Stewart- 23 October, 2009<br>Kristina Carroll, Ph.D.- 15 January, 2013 |

# 1. Introduction

Flublok is a trivalent vaccine for the prevention of influenza illness in persons 18-49 years of age caused by the influenza strains represented in the vaccine. It is supplied as a sterile, aqueous buffered solution in single-dose vials for intramuscular injection. Four properties of Flublok are different from other U.S.-licensed, trivalent influenza vaccines. First, the Flublok active ingredients are a mixture of recombinant, purified, hemagglutinin (HA) proteins from the A influenza subtypes and B influenza type instead of a mixture of live attenuated viruses or inactivated "split" or "subunit" virus subtypes prepared from whole influenza viruses. Second, Flublok is the first influenza vaccine produced in insect cells (*Spodoptera frugiperda*) and it does not depend upon the use of eggs at any stage of its manufacture. Third, the vaccine is formulated to have a potency of 45 mcg/0.5 mL dose for each of the 3 influenza strains in contrast to the 15 mcg/dose potency per strain for inactivated, trivalent vaccines. Finally, the shelf life of Flublok is 16 weeks compared to the typical 12 month shelf-life for most of the inactivated, trivalent influenza vaccines. A Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was held on November 19, 2009, to discuss the safety and efficacy of Flublok in persons 18 years and older.

# 2. Background

Protein Sciences Corporation (PSC) submitted a Biologics License Application (BLA) for Flublok on April 17, 2008, under the provisions for accelerated approval. A 6 month priority review was requested and was granted. Clinical development of Flublok was conducted under IND 11951 submitted on September 22, 2004, with clinical studies conducted in the U.S. The product was granted a Fast-track status on December 11, 2006, and CBER held a pre-BLA meeting with PSC in September 2007 to discuss the BLA submission process. After completing the review of the original BLA submission and amendments submitted in response to several requests for additional information, CBER issued a Complete Response (CR) letter on August 29, 2008, due to inadequacy of the clinical, statistical and chemistry, manufacturing and control (CMC) data submitted to support licensure. PSC submitted a response to the August 29, 2008 CR letter on April 27, 2009, and requested traditional approval based on new clinical endpoint efficacy data that had become available since the initial filing of the BLA and which was included in their response. After completing review of this resubmission, CBER issued a second CR letter on January 11, 2010, due to unresolved CMC issues identified in the first CR letter. On April 19, 2010, CBER held a face-to-face meeting requested by PSC to define a path to address CBER's concerns. On June 29, 2010, PSC submitted a response to the January 11, 2010 CR. In a July 27, 2010 teleconference, CBER informed PSC that their June 29, 2010 submission was not complete and that the review clock had not been restarted. CBER worked with PSC for the next 24 months to address CBER's concerns, primarily concerns due to ---(b)(4)--- present in Flublok (originating from the *Spodoptera frugiperda* cells) and manufacturing process validation. PSC submitted their complete response to the January 11, 2010 CR letter on July 16, 2012, and this resubmission started a new 6-month review clock.

There is no foreign marketing experience with Flublok.

# 3. Chemistry Manufacturing and Controls (CMC)

### a) Product Quality

ExpresSF+ cells

The *expres*SF+ (SF+) cell line used for recombinant HA protein expression is a non-transformed, non-tumorigenic, continuous insect cell line. This cell line was adapted to grow in serum-free medium by PSC from Sf9 cells obtained from the American Type Culture Collection and originated from the fall armyworm, *Spodoptera frugiperda*. ----------
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Master and Working Baculovirus Banks

Expression of the recombinant HA proteins is achieved by infection of *Spodoptera frugiperda* SF+ cells with a baculovirus working virus bank (WVB) into which the HA gene from a CDC-provided influenza virus is inserted. ----------
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**Manufacturing summary**

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Drug Product (DP)- The monovalent bulks are shipped to Hospira, Inc. (a contract facility used for final formulation and filling) under controlled conditions for formulation and filling. Monovalent bulks containing HA proteins from each of the 3 influenza strains are blended with buffer to produce a trivalent drug product. ----------(b)(4)---------- PSC chose to release the final filled Flublok product and CBER agreed. This is in contrast to most U.S.-licensed, trivalent inactivated influenza vaccines for which the trivalent bulks are released.

In addition to the testing performed on the MCB, WCB, MVB and WVB to support the absence of adventitious agents, clearance studies demonstrated adequate removal of model viruses by the purification process. In addition, the process removes the baculovirus vector; this is confirmed through testing ----------(b)(4)----------.

CBER identified several upstream and downstream process validation deficiencies and product specification inadequacies in the original BLA submission. These were communicated to PSC in CBER's August 29, 2008 CR letter. Many of the deficiencies were corrected in PSC's initial response to the August 29, 2008 CR letter. However, the unresolved issues required issuance of a second CR letter to PSC on January 11, 2010. A face-to-face meeting was held on April 19, 2010, to determine a strategy for PSC to address CBER's concerns. CBER worked with PSC in a rolling review process during which several amendments were submitted by PSC in response to CBER advice and information requests to resolve the outstanding manufacturing problems. Upon review of the information submitted in PSC's July 16, 2012 response to CBER's second CR letter, CBER concluded that Flublok process validation, manufacturing consistency, in-process controls and testing and specifications are adequate to support licensure.

Flublok is formulated to contain 45 mcg HA per influenza strain for a total HA content of 135 mcg/0.5 mL dose. The product is preservative-free, non-adjuvanted and contains no egg proteins. The composition of the final product is shown in Table 1.

**Table 1. Flublok Final Product Composition**

| Ingredients | Quantity per 0.5 mL dose |
|---|---|
| Active Ingredients<br>Recombinant hemagglutinin (HA) proteins from the influenza virus strains | <br>45 mcg recombinant HA per influenza strain |
| Excipients<br>Sodium chloride<br>Monobasic sodium phosphate<br>Dibasic sodium phosphate<br>Polysorbate 20 | <br>4.4 mg<br>0.195 mcg<br>1.3 mg<br>27.5 mcg |

-------(b)(4)--------- and Drug Product Testing- The release specifications for Flublok --------- (b)(4)---------- and trivalent final product are shown in Table 2.

**Table 2. Flublok ----(b)(4)---------- and Trivalent Product Release Specifications**

| **Test and Method** | **------(b)(4)----------<br>----------(b)(4)----------** | **Drug Product<br>(Trivalent Vaccine) Specifications** |
|---|---|---|
| -------(b)(4)----------<br>---------- | ---(b)(4)----- | (b)(4) |
| Endotoxin ---(b)(4)----- | ----------(b)(4)---------- | ---(b)(4)------- |
| Sterility (21 CFR 61.12) | (b)(4) | No growth ≥ 14 days |
| Total DNA ---(b)(4)---- | ----------(b)(4)---------- | < 10 ng/dose |
| ------(b)(4)---------- | ----------(b)(4)---------- | (b)(4) |
| Triton X-100 ---(b)(4)---- | (b)(4) | ---(b)(4)--- |
| General Safety (21 CFR 610.11) | (b)(4) | All animals survive and weigh no less than at time of injection |
| Host Cell Protein<br>---(b)(4)----- | (b)(4) | (b)(4) |
| Purity -------(b)(4)----------<br>--------- | (b)(4) | (b)(4) |
| Purity ------(b)(4)----------<br>---------- | (b)(4) | (b)(4) |
| Potency (SRID) | ----(b)(4)-------- | ----------(b)(4)----------<br>---- |
| Identity -(b)(4)-- | ----------(b)(4)----------<br>---------- | ----------(b)(4)----------<br>---------- |
| Appearance<br>-------(b)(4)----------<br>------- | ----------(b)(4)----------<br>-------- | Clear, colorless liquid essentially free of visible particles |
| (b)(4) | ---(b)(4)--- | ---(b)(4)--- |
| -----(b)(4)----- | ----(b)(4)----- | (b)(4) |
| Total Protein Content (BCA) | ----(b)(4)----- | ≤ 285 mcg/dose[3] |
| -------(b)(4)----------<br>---------- | (b)(4) | ---(b)(4)--- |
| ---(b)(4)------ | (b)(4) | -------(b)(4)---------- |
| Fill Volume | (b)(4) | ---(b)(4)--- |
| --------(b)(4)----------<br>---------- | ----------(b)(4)----------<br>---------- | (b)(4) |

[1] N/A = not applicable
[2]Lower limit at expiry is ----(b)(4)----- for each recombinant HA
[3]Average of (b)(4) determinations

Residual components- Each 0.5 mL dose of Flublok may contain residual amounts of baculovirus and host cell proteins [≤ 10% of total protein (≤ 28.5 mcg)], baculovirus and cellular DNA (≤ 10 ng), and Triton X-100 (≤ 100 mcg).

Product Stability and Shelf Life- Following review of the Flublok stability data, CBER determined that the data supported a 16 week shelf life (from the date of manufacture) of Flublok when stored at 2-8°C. The Flublok date of manufacture is defined per 21 CFR 610.50(b)(5) as the date of final sterile filtration.

Potency- Flublok potency is measured using the single radial immunodiffusion (SRID) assay. PSC agreed to use CBER-approved reagents *(i.e.*, egg-based reference antigens and sheep antiserum raised against HA purified from egg-grown virus) in the potency assay. ----------(b)(4)----------.

PSC was unable to use CBER reference antigen to determine the potency of monovalent bulks or trivalent product containing recombinant H1 HA protein of A/California/07/2009 (2009 H1N1pdm). CBER confirmed that the available reference antigens were not suitable for potency determination of this HA. PSC demonstrated the native structure of the 2009 H1N1pdm recombinant HA protein and thus, CBER agreed that PSC's recombinant H1 HA be used as reference antigen instead of the egg-based H1 reference antigen. This recombinant HA was aliquoted, lyophilized and calibrated by CBER. Both CBER and PSC are monitoring the stability of this reference antigen. Egg-based H3 and B influenza reference antigens are used to measure Flublok potency for the recombinant H3 and B strain HA proteins in the 2012-2013 vaccine. CBER-approved HA-specific sheep antiserum is used in all SRID assays. CBER has requested that PSC include data to support the use of reference reagents when strain change information is submitted.

Purity- The purity of recombinant HA in ----(b)(4)---------- is measured ----------(b)(4)----------. At the pre-BLA meeting, PSC noted difficulty in achieving levels of purity usually expected of recombinant proteins when using a universal manufacturing process. It was agreed that the ---(b)(4)--------- purity specification would be(b)(4), but that the product should be formulated to have (b)(4) purity (a value calculated based on the ratio of individual components in the drug product).

Hemagglutination Inhibition Assay (HAI) Assay- HAI assays were used in Flublok clinical studies to assess immunogenicity by measuring serum titers of antibodies against the recombinant HA proteins in the vaccine. These titers were used to determine the proportion of subjects achieving a minimum 4-fold rise in pre- *versus* post-vaccination antibody titer (*i.e.*, the seroconversion rate) and the percentages of subjects with post-vaccination HAI antibody titers ≥ 1:40. These criteria are used as co-primary endpoints for HAI antibody titers to each viral strain contained in the vaccines as per CBER guidance for seasonal influenza vaccines. In the pre-BLA meeting, CBER and PSC agreed to the use of the recombinant HA proteins in place of the egg-based influenza HA antigens typically used in this assay. The HAI assay validation data were subsequently reviewed by CBER product, bioassay and statistical reviewers and were found to be limited. Of note, data showed that antibody titers measured using the recombinant HA proteins tended to be higher than those measured using egg-derived antigens and that the titer difference was influenza strain dependent. Thus, absent further testing, CBER determined

that seroconversion rates measured in this assay cannot be used to predict protection from influenza disease.

**b) CBER Lot Release**

The lot release protocol template for the final filled product was submitted to CBER for review on January 2, 2013, and was found to be acceptable. Samples from 3 lots of each of the 3 recombinant HA monovalent bulks and samples from 3 lots of final filled product together with SRID potency test results will be provided to CBER for testing at the start of each influenza season. PSC and CBER agreed that only the final filled Flublok product will be released by CBER.

**c) Facilities review/inspection**

Two facilities are used to manufacture Flublok:

Protein Sciences Corporation
1000 Research Parkway
Meriden, CT 06450, USA
Field Establishment Identification Number: 3002969304

Hospira, Inc.
1776 North Centennial Drive
P.O. Box 1247
McPherson, KS 67460, USA
Field Establishment Identification Number: 1925262

Manufacture of the Flublok recombinant HA monovalent bulks is conducted at the Meriden, CT facility. A pre-license inspection conducted at this facility from July 7-11, 2008, resulted in numerous objectionable conditions requiring a follow-up inspection after corrections were instituted. The follow-up inspection was conducted from October 19-23, 2009, and an FDA Form 483 was issued following this inspection. Because more than two years had passed between the follow-up inspection and PSC's July 16, 2012 response to CBER's January 11, 2010 Complete Response letter, CBER conducted a third inspection of the Meriden, CT facility from November 5-9, 2012. An FDA Form 483 was issued following this inspection. CBER review of the information provided in response to the 483 forms indicated that all items cited were adequately addressed. The compliance status of this site is deemed acceptable and the inspection was designated Voluntary Action Indicated (VAI); no issues were found that would impact the approval of the BLA.

The monovalent bulks are shipped to the contract manufacturer, Hospira, Inc. for formulation, filling and some release testing. The remaining release testing, including product potency, is conducted by PSC at the Meriden, CT facility. Inspections of Hospira were waived based on CBER SOPP 8410 because previous inspections at this facility occurred within two years of inspections scheduled for Flublok and the inspection reports supported the overall compliance status of this contract manufacturer.

**d) Environmental Assessment**

PSC requested a Categorical Exclusion from the requirement for an Environmental Assessment based on 21 CFR 25.31(c) because influenza hemagglutinin is a substance that occurs naturally in the environment and approval would not alter significantly the concentration or distribution of the hemagglutinin, its metabolites, or degradation products in the environment. CBER agreed that the request was justified and that there were no extraordinary circumstances that would require an environmental assessment.

# 4. Nonclinical Pharmacology/Toxicology

Because the target population for Flublok includes females of childbearing potential and because Flublok may be recommended for use in pregnant women, PSC conducted a GLP reproductive toxicity study of Flublok in rats in accordance with 21 CFR 312.23(a)(8). The study was designed to evaluate potential adverse maternal and developmental effects when administered to female rats twice prior to mating and once during gestation. CBER concluded that the results of the study indicated that, at a dose of approximately 300 times the human dose (on a mg/kg basis), Flublok did not affect embryonic or postnatal development and did not exert teratogenic effects. PSC requested and CBER concurred that Flublok be designated pregnancy category B in Section 8.1 of the Flublok package insert.

# 5. Clinical Pharmacology

No clinical pharmacology or pharmacokinetic studies were performed in the clinical development program for Flublok.

# 6. Clinical/Statistical Effectiveness

The BLA contained data from four clinical studies to support licensure. Study PSC04 provided the pivotal safety and efficacy data to support approval of Flublok for use in persons 18 through 49 years of age. Study PSC01, a dose finding study, also provided safety data on Flublok. Studies PSC03 and PSC06 were immunogenicity and safety studies intended to support licensure in persons 50 years of age and older.

PSC04:
PSC04 was a Phase 3 randomized, double-blind, placebo-controlled, clinical endpoint efficacy and safety study in 4648 healthy adults aged 18 to 49 years conducted in the U.S. during the 2007-2008 influenza season. This study also assessed clinical lot consistency by evaluating post-vaccination anti-HAI geometric mean titers in a subset of subjects. Subjects were first randomized 1:1 to receive Flublok or saline placebo. The Flublok group was then further randomized 1:1:1 to receive vaccine Lot A, Lot B or Lot C.

The primary clinical efficacy endpoint was culture-confirmed, symptomatic Centers for Disease Control and Prevention (CDC) influenza-like illness (ILI) which the protocol defined as the presence of fever ≥100ºF accompanied by sore throat, coughing or both on the same or on consecutive days and due to strains antigenically matched to the vaccine strains. Note that this

definition of "CDC-ILI" is slightly modified from the case definition of ILI as defined by the CDC (temperature of 100°F [37.8°C] or greater and a cough and/or a sore throat in the absence of a known cause other than influenza). The secondary clinical efficacy endpoint was culture-confirmed ILI due to strains antigenically matched to the strains represented in the vaccine. Flu symptom criteria for an ILI (as distinguished from "CDC-ILI" for the primary endpoint) were met by having at least one symptom from any 2 of the following 3 groups of symptoms: 1) fever of 100°F or higher; 2) cough, sore throat, runny nose, or stuffy nose; or 3) muscle or joint aches, headache, chills/sweats, or tiredness/malaise. Active and passive surveillance for ILI was conducted during the 2007-2008 influenza season. Nasal and throat swabs were taken from subjects reporting ILIs and evaluated for influenza virus isolation by culture.

The pre-defined success criterion for the primary efficacy analysis was that the lower bound of the 95% confidence interval (CI) of vaccine efficacy should be at least 40%. Vaccine efficacy against culture-confirmed modified CDC-ILI (as defined above) due to antigenically matched influenza strains could not be determined reliably because 96% of the influenza isolates obtained from subjects in Study PSC04 were not antigenically matched to the vaccine strains.

The results of pre-specified and post-hoc exploratory analyses of vaccine efficacy in preventing ILI due to any influenza virus strain, regardless of antigenic match to the vaccine strains are shown in Table 3. The pre-specified endpoint was for modified CDC-ILI as defined above while the post-hoc endpoint was for any culture positive ILI, regardless of meeting the modified CDC-ILI definition.

**Table 3: Vaccine Efficacy against Culture-Positive ILI Due to Any Influenza Strain**

| | **Total number of subjects** | **Number of subjects with culture-positive ILI*** | **Vaccine Efficacy* (%)** | **95% CI* (%)** |
|---|---|---|---|---|
| Flublok | 2344 | 44<br>(64) | 44.6<br>(44.8) | 18.8 to 62.2<br>(24.4 to 60.0) |
| Placebo | 2304 | 78<br>(114) | --<br>-- | --<br>-- |

Source: BLA 125285 Amendment 12, Volume 2, Tables 24 and 25, p 83 and 85

* Data in parentheses are for the post-hoc endpoint while data not in parentheses are for the pre-specified endpoint

Considering that the efficacy of Flublok in preventing ILI due to antigenically matched strains is expected to be at least as high as that observed in preventing ILI due to any influenza strain, CBER concluded that the efficacy data from Study PSC04 (Table 3) were adequate to support licensure of Flublok for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine in adults 18 through 49 years of age.

In Study PSC04, pre-specified clinical lot consistency criteria based on post-vaccination geometric mean anti-HA antibody titers were met for the H1 and B strains but not for the H3 strain. However, PSC and CBER subsequently determined that two of the Flublok lots used in Study PSC04 contained a lower amount of HA from influenza virus H3N2 relative to that in the third lot. Subsequently, PSC revised the Flublok formulation specifications to ensure equal amounts of the three HA antigens in the final vaccine.

Studies PSC06 and PSC03:
PSC06 and PSC03 were Phase 3, randomized, active-controlled (Fluzone), clinical endpoint efficacy studies conducted in U.S. adults 50 to 64 years of age and adults 65 years of age and older, respectively. The clinical efficacy data from these studies were inadequate to support approval of Flublok for use in these age groups because too few culture-confirmed cases of influenza were identified. In view of concerns regarding the reliability of the HAI assay in the evaluation of HAI antibody seroconversion (as discussed previously), CBER determined that the immunogenicity data from these studies were inadequate to support traditional approval of Flublok for use in these age groups.

PSC01
This was a Phase 2, randomized, modified, double-blind, placebo-controlled, dose finding, safety, immunogenicity, and efficacy study of 458 healthy adults aged 18 to 49 years conducted at three centers in the U.S. This study compared immune responses elicited from 75 mcg (15 mcg recombinant H1 HA, 45 mcg recombinant H3 HA and 15 mcg recombinant B HA) and 135 mcg (45 mcg of each of the 3 recombinant HA proteins) doses of Flublok. PSC concluded that the 135 mcg dose of Flublok was required for an adequate antibody response and used this dose for the PSC04, PSC06 and PSC03 studies. The point estimate of vaccine efficacy (75.4%) in this study in the prevention of culture-confirmed, modified CDC-ILI suggested a favorable trend. However, the study was small and not statistically powered to demonstrate vaccine efficacy, cases of modified CDC-ILI were few (Flublok = 1, placebo = 4), and the CIs of the point estimate were wide and included zero.

**Biomonitoring Review**- Three sites were inspected by Bioresearch Monitoring. CBER concluded that the inspections did not reveal any problems that would impact the data submitted in the BLA.

**Pediatric Research Equity Act (PREA)**- PSC submitted a pediatric plan on September 13, 2012, with a request for a waiver in subjects 0-6 months of age. PSC also requested a waiver in pediatric subjects 6 through 35 months of age due to a clinical study (PSC02) showing Flublok to be ineffective in that population. PSC's pediatric plan was presented to the Pediatric Review Committee (PeRC) on October 24, 2012, and the PeRC agreed with a waiver in persons 0 through 35 months of age (because Flublok is unlikely to be effective in this age group) and a deferral of studies in persons 3-5 years old and 6-17 years old. The PREA required studies specified in the approval letter and agreed upon with PSC are as follows:

1. Deferred pediatric safety, reactogenicity and immunogenicity study (Study PSC08) under PREA for active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in Flublok, in children ages 6 years through 17 years.

2. Deferred pediatric safety, reactogenicity and immunogenicity study (Study PSC14) under PREA for active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in Flublok, in children ages 3 years through 5 years.

# 7. Clinical Safety

The total safety database of persons receiving a single, 0.5 mL, 135 mcg dose of Flublok from the 4 studies described above was 3233 subjects (2497 subjects 18 through 49 years of age, 300 subjects 50 through 64 years of age and 436 subjects ≥ 65 years of age). The numbers of subjects in the active control (Fluzone) and saline placebo recipients were 735 and 2458, respectively. The frequencies of the most common local and systemic solicited adverse events (injection site pain, headache, fatigue and myalgia) occurring within 7 days of injection in Flublok and Fluzone control recipients differed by ≤ 2%. Flublok and Fluzone recipients experienced significantly more local injection site pain than did placebo recipients (37% and 36%, respectively versus 8%). The rates of other solicited local and systemic adverse events (AEs) in Flublok recipients as compared to placebo recipients were similar, differing by ≤ 3%. No unusual trends or patterns were observed for these adverse events and most events were assessed as mild or moderate.

A total of 3 deaths occurred in Flublok recipients in the 4 clinical studies. A 47 year old subject in study PSC04 died of a pulmonary embolus 95 days following vaccination. An 80 year old subject in study PSC03 died of a perforated viscus with secondary peritonitis 4 days following vaccination. An 89 year old subject in study PSC03 died of a pontine hemorrhage 92 days following vaccination. None of the deaths were considered by the investigators or CBER to be vaccine-related. Three deaths were also reported across the control groups.

Overall, 90 serious adverse events (SAEs) were reported in 70 Flublok recipients and 90 SAEs were reported in 71 Fluzone or placebo controls across studies. Among subjects 18-49 years of age in study PSC04, serious adverse events SAEs occurred in 7 (0.3%) Flublok and 12 (0.5%) placebo recipients within 28 days of vaccination. One SAE was considered possibly related to Flublok: pleuropericarditis occurring 11 days following vaccination in a 47 year old male. No specific cause was identified. The remaining 6 Flublok SAEs (viral hepatitis, hand fracture, uterine leiomyoma, iron deficiency anemia, bipolar disorder, and acute pyelonephritis) were not considered by the investigator or CBER to be related to the vaccine. In study PSC01, 2 SAEs were reported among 153 Flublok recipients and none among the 154 placebo recipients. Neither SAE was considered related to Flublok including the case of hypoglycemic seizure in a 20 year old female that occurred 26 days following vaccination. Among subjects 50-64 years of age (PSC06), SAEs occurred in 1 (0.3%) Flublok and no Fluzone recipients within 28 days of vaccination. Vasovagal syncope occurred in the Flublok recipient within 10 minutes of vaccination and was attributed to the intramuscular injection. Among subjects 65 years of age and older, 42 SAEs were reported by 34 (7.8%) Flublok recipients and 45 SAEs were reported by 36 (8.3%) Fluzone recipients over the 6 months following vaccination. Considering the clinical characteristics of these events including time of onset in relation to vaccination, none of the Flublok SAEs were considered by the investigators or CBER to be caused by the study vaccine. Only one subject was discontinued due to a possible vaccine-related AE, the case of pleuropericarditis.

No cases of Guillain-Barré syndrome, oculorespiratory syndrome or anaphylaxis were reported among Flublok recipients. There was one hypersensitivity event that occurred in a 22 year old female Flublok recipient with a history of atopy that appeared related to the vaccine. Abrupt onset of lip and tongue swelling, described as non-serious and moderate in intensity, occurred approximately 10 hours post-vaccination. Her symptoms responded to self-medication with

antihistamines which she had at home and resolved by the next day. There were no other allergic reactions that appeared related to Flublok, and there was no imbalance of these reactions between Flublok and control groups across studies.

CBER concluded that the safety data supported approval of Flublok for use in adults 18 through 49 years of age. As described in Section 11 below, PSC has committed to conduct a post-marketing observational study to further characterize the safety profile of Flublok in this population. Although no safety concerns were identified in persons 50 years of age and older, the size of the safety database in the older adult populations (50-64 years of age and 65 years of age and older) was considered insufficient to support licensure for a novel vaccine.

## 8. Advisory Committee Meeting

Flublok was the subject of a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting held on November 19, 2009. The committee voted 9 to 2 that the data supported Flublok effectiveness in adults 18 through 49 years of age, but voted that the data did not support effectiveness in adults 50 years and older. The committee was divided, voting 5 to 6 that the safety data did not support licensure for use in adults 18 years of age and older. However, negative votes regarding the safety data primarily reflected concerns regarding the relatively small size of the safety database in persons 50 years of age and older.

## 9. Other Relevant Regulatory Issues

None.

## 10. Labeling

PSC submitted revised versions of the package insert (PI) and carton/container labels in response to a CBER request after CBER determined that the approval of the Flublok BLA would be for persons 18 through 49 years of age. The revised PI and carton/container labels were reviewed by the clinical, statistical, product and Advertising and Promotional Labeling Branch (APLB) reviewers. Final versions of the labeling were agreed upon through discussions with PSC and were submitted in Amendments 74 and 76.

## 11. Recommendations and Risk/Benefit Assessment

**a) Recommended Regulatory Action-** Based upon the review of the clinical and product data submitted with the original application and provided in response to the Complete Response letters, it is the recommendation of the review committee to license Flublok for active immunization against influenza disease caused by influenza virus subtypes A and type B represented in the vaccine in persons 18-49 years of age.

**b) Risk/Benefit Assessment**- The data provided with the original application and submitted in response to the CBER's CR letters support the clinical effectiveness of Flublok in persons 18 through 49 years of age. In a clinical endpoint efficacy trial (PSC04), efficacy of Flublok was demonstrated against influenza disease caused by strains not necessarily antigenically matched to

the strains contained in the vaccine (Table 3). The most common risks associated with Flublok are injection site pain, headache, fatigue and myalgia. These events are generally mild, resolve within a few days and have been associated with other U.S.-licensed inactivated influenza vaccines. CBER identified no serious safety risks thought to be due to Flublok.

CBER concluded that the risk associated with Flublok due to ---(b)(4)----- is remote based upon the comprehensive testing performed by PSC.

**c) Recommendation for Postmarketing Risk Management Activities-** There was no recommendation for postmarketing risk management activities. See below for the postmarketing activities associated with the licensure of Flublok.

**d) Recommendation for Postmarketing Activities-** As discussed in Section 6 above, PSC is required to conduct two postmarketing pediatric studies in accordance with PREA under Section 505B(a) of the Food Drug and Cosmetic Act (FDCA). PSC has also committed to two clinical studies to be conducted by PSC as postmarketing commitments subject to 21 CFR 601.70 and one postmarketing study commitment not subject to 21 CFR 601.70. These postmarketing activities to be included in the approval letter and agreed upon with PSC are shown below:

<u>Postmarketing Requirements under Section 505B(a) of the FDCA:</u>

1. Deferred pediatric safety, reactogenicity and immunogenicity study (Study PSC08) under PREA for active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in Flublok, in children ages 6 years through 17 years.
   Final Protocol Submission: April 30, 2013
   Study Completion Date: November 30, 2014
   Final Report Submission: November 30, 2015

2. Deferred pediatric safety, reactogenicity and immunogenicity study (Study PSC14) under PREA for active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in Flublok, in children ages 3 years through 5 years.
   Final Protocol Submission: June 30, 2015
   Study Completion Date: June 30, 2016
   Final Report Submission: June 30, 2017

<u>Postmarketing Commitments subject to reporting requirements of 21CFR 601.70:</u>

3. To establish a pregnancy registry to collect data prospectively on an actively recruited cohort of 600 pregnant women, of whom at least 300 will have been exposed to Flublok. The statistical analysis will include both exposed women and concurrently enrolled women unexposed to Flublok, and it will be adjusted to control for important covariates.
   Final Protocol Submission: June 30, 2013
   Study Completion Date: December 31, 2019
   Final Report Submission: December 31, 2020

4. To conduct an observational postmarketing safety study in approximately 25,000 Flublok recipients aged 18 to 49 years to further characterize the safety profile of Flublok using recipients of egg-based, trivalent inactivated influenza virus vaccine as a comparator with appropriate adjustment or matching for important covariates such as sex and age.

    Final Protocol Submission: March 31, 2013
    Study Completion Date: May 31, 2014
    Final Report Submission: May 31, 2015

Postmarketing Study not subject to reporting requirements of 21 CFR 601.70:

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