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Subject: Addendum: phase 4 observational safety study; pregnancy registry

Applicant: Protein Sciences Corporation (PSC)

Product: Trivalent recombinant hemagglutinin influenza vaccine (rTIV); *Spodoptera frugiperda* cell line; Flublok

STN 125285.0

Proposed Indication: For active immunization of adults 18-49 years of age, against influenza disease caused by influenza virus subtypes A and type B represented in the vaccine

Submission type Biologics License Application

Submission Date: September 21, 2012

Action Due Date: January 16, 2013

1. Introduction

a. Product Description(from the proposed package insert)

Flublok consists of three highly purified full-length recombinant influenza hemagglutinin proteins that are produced in a non-transformed, non-tumorigenic continuous cell line (expresSF+ insect cells) that is derived from Sf9 cells of the fall armyworm, *Spodoptera frugiperda*, and grown in serum-free medium composed of chemically-defined lipids, vitamins, amino acids, and mineral salts. Each of the three recombinant hemagglutinins is expressed in this insect cell line using a viral vector (baculovirus *Autographa californica* Nuclear Polyhedrosis Virus). The individual hemagglutinins are extracted from the cells with buffer and detergent and further purified by column chromatography. No antibiotics are used during the manufacturing process. The highly purified hemagglutinins are then blended and filled into single-dose vials. Flublok is standardized according to USPHS requirements for the 2012 - 2013 influenza season and is formulated to contain 135 mcg of hemagglutinin per 0.5 mL dose in the recommended ratio of 45 mcg rHA of each of the following 3 strains: A/California/7/2009 (H1N1), A/Victoria/361/ 2011 (H3N2), and B/Wisconsin/1/2010. This concentration of the active

ingredient is three times higher than trivalent inactivated vaccines. No preservatives are added. A single 0.5 mL dose of Flublok contains 150 mM sodium chloride, 10-20 mM sodium phosphate, and 0.005% polysorbate 20 (Tween 20). Each dose of Flublok may also contain residual amounts of insect cell and viral protein (not more than 10%) and baculovirus and cellular DNA (not more than 10 ng per 135 mcg dose) from the manufacturing process. Flublok contains no egg proteins. The stoppers used for the single-dose vials contain no latex.

b. Objectives and scope of this review

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies should the product be licensed. The pharmacovigilance plan and safety database were previously reviewed by the Division of Epidemiology on December 14, 2009. No additional safety data has been provided by the sponsor to date. However, in the interim PSC has proposed and/or made revisions to the previously proposed pharmacovigilance activities intended to evaluate safety after product licensure. These activities, which will be reviewed in this memorandum, fall into three general categories: general safety in adults aged 18-49 years, general safety in adults aged ≥ 50 years, and pregnancy outcomes.

2. Regulatory history

April 18, 2008: original submission

August 29, 2008: Complete Response letter

April 7, 2009: sponsor responded

November 19, 2009: advisory committee meeting (committee voted 9-2 that data supported effectiveness in adults 18-49, but not adults ≥ 50 years of age; voted 6-5 that clinical evidence was not adequate to support safety in adults ≥ 18 years of age)

January 11, 2010: Complete Response letter was sent to the sponsor. This letter noted eight separate concerns associated predominantly with manufacturing, product purity and shelf life, antigenic analysis, and product containers. Although the advisory committee voted that the clinical evidence was not adequate to support safety in adults ≥ 18 years of age, the Complete Response letter did not request additional clinical safety data. The following was stated regarding Pharmacovigilance: "We acknowledge that you have included a Pharmacovigilance plan in your BLA; however, we reserve our comments on this proposal for later, when this application is found suitable for approval. Depending on subsequent CBER evaluation and final labeling, CBER may request additions to the Pharmacovigilance plan."

July 16, 2012: sponsor resubmission for a Biologics License Application for trivalent recombinant hemagglutinin influenza vaccine, for the active immunization of adults 18 years of age and older against influenza disease. The sponsor provided no new clinical safety data.

3. Materials reviewed in support of this application

a. Prior Division of Epidemiology review memo

Since there are no new clinical data to support safety, we reviewed the information that was previously provided and reviewed by our division. On December 14, 2009, with concurrence from Robert P. Wise, MD, MPH (Deputy Division Director) and Rickey Wilson, MD, JD (Division Director), Patricia J. Rohan, MD signed a OBE/DE memo (125285 Flublok DE Rev Rnl signed.pdf, located in the CBER Electronic Data Room) that reviewed the clinical study reports, interim clinical study reports, pharmacovigilance plan, responses to clinical comments, final clinical study reports, appendices (safety data), and pediatric development plan.

b. Comments from the clinical reviewer

c. Responses to information requests sent by the Division of Epidemiology (subsequent to BLA resubmission July 2012) regarding pharmacovigilance activities proposed by PSC

4. Conclusions and observations from prior Division of Epidemiology review

a. Safety database

The database is limited by the relatively small size (N = 3233 exposed to Flublok 135 ug), a predominantly Caucasian population (73% of Flublok subjects), and relatively few data from older adults (median subject age 37 years) and from pregnant women.

b. Safety concerns

- i.** No specific safety issues that would trigger a Title IX required postmarketing study were identified. However, the VRBPAC vote highlighted the limitations of the postlicensure safety database.
- ii.** The reviewer highlighted missing information related to older adults and pregnant women.

c. Proposed phase 4 general safety study

The DE reviewer summarized the sponsor's prior plan as follows:

PSC07/09: A Phase 4 open label multi-center study comparing safety and immunogenicity of Flublok to FLUZONE over 2 successive influenza seasons in 100,000 adults ≥ 18 years of age, with and without high risk medical conditions within the Northern California Kaiser Permanente clinic system. Approximately half of the individuals will receive either Flublok or a US-licensed egg-derived vaccine (TIV), and monitored, via electronic medical record review, for clinically significant AEs. The only subjects excluded for medical reasons will be those with contraindications for receipt of the respective influenza vaccines. An attempt will be made to use the same TIV throughout the study, or at least within a season.

A subset of subjects (10,000) will receive telephone interviews to capture local and systemic post vaccine reactions.

Subjects will be monitored for medically attended events, including clinic or emergency department visits and/or hospitalizations. Using a retrospective cohort design with self-control analytical approach, detection of significant AEs for each cohort will be based on risk windows of 0 to 3 days, 1 to 14 days (primary analysis), 1 to 42 days, and 15 to 42 days after vaccination, and compared with two control periods: one before vaccination (days -56 to -15 for the primary analysis [to exclude "healthy vaccinee" effects]) and the second after the risk window (days 15-28 for the primary analysis). All individual ICD-9 codes as well as predefined aggregate codes will be examined. Any diagnoses which appear to occur more frequently in a risk window based on electronic review will be further assessed via medical chart review. The final protocol for this study

(including a statistical analysis plan) will be submitted within 12 months following Flublok approval and will be scheduled shortly thereafter. Data will be analyzed annually, with the final study report to be submitted by December 31, 2013. Protocol was to have been submitted within 12 months of Flublok accelerated approval.

d. Pregnancy safety monitoring

The sponsor did not propose a prospective study in pregnant women but stated that spontaneous reports indicating vaccination during pregnancy would trigger followup.

5. Safety conclusions and observations from the clinical reviewer

a. Proposed phase 4 general safety study

In her “Summary of outstanding clinical issues to be discussed in the review team meeting June 20, 2012,” Cynthia Nolletti, MD (clinical reviewer) stated:

Main Clinical Reviewer Conclusions:

If traditional approval is to be granted in adults 18 to 49 years of age, PMRs and PMCs for additional safety and efficacy studies should be requested for the following reasons:

- *Flublok is a novel vaccine and should meet a higher standard than a minimal safety database of 3000 subjects;*
- *Concerns regarding the possibility of an increased risk for hypersensitivity or idiosyncratic events, such as the case of pleuropericarditis*
- *Traditional approval in adults 50 to 64 of age and 65 years and older should not be granted because of insufficient safety and vaccine efficacy data (Dr. Baylor and review team agreed on this approach after VRBPAC*

b. Pregnancy safety

Regarding pregnancy, Dr. Nolletti summarized prelicensure outcomes as follows: in study PSC04, 20 Flublok recipients became pregnant, and 15 had complete follow-up. Ten pregnancies had normal outcomes. Adverse events included hyperemesis, pulmonary embolism, *Staphylococcus* infection, and miscarriage. Dr. Nolletti remarked that 25% pregnancies in the Flublok group lacked follow-up information, but she added that, among the other 75%, the data did not suggest an imbalance of vaccine-related adverse events

6. Additional information (subsequent to BLA resubmission July 2012) related to general safety studies

In an Information Request (IR) on September 28, CBER asked whether the sponsor still intended to perform a large, Phase 4, comparative safety and immunogenicity study and, if so, whether PSC could please provide any updates. On October 15, the sponsor responded as follows.

Study design and data collection (copied verbatim from PSC’s response to the IR):

It is our intention to distribute approximately 125,000 doses of Flublok to young adults 18-49 years of age in selected locations and through healthcare organizations under controlled conditions in January – February 2013 assuming approval is obtained. These focused efforts will include individuals who may include [sic] those with underlying medical conditions that were excluded from PSC01 and PSC04. Pharmacovigilance, as described in the BLA, will be emphasized to participants and healthcare providers to gather information on adverse events that may be associated with Flublok. The safety information from the young adult population will be gathered from selected locations and healthcare organizations where the vaccine is administered. We intend to collect sufficient information from vaccine recipients to allow follow-up. This data will be carefully evaluated and serve as the basis for further Phase IV studies should those be needed.

In addition, we anticipate conducting PSC11, a blinded, comparative trial of short-term safety of Flublok vs. Fluzone in ~2,500 adults ≥50 years of age. As this study is proposed to collect short-term safety only, we can enroll individuals who received licensed inactivated influenza vaccine at least 30 days prior to enrollment. PSC11 will allow enrollment of individuals with underlying medical conditions and assess safety of Flublok in individuals who may have been excluded from the PSC03 and PSC06 trials. It is our intention to conduct a clinical efficacy trial of Flublok vs. Fluzone in ~2,500 – 3,000 adults of the same age group prior to the next influenza season, potentially 2013-2014. These subjects, who will include those with underlying medical conditions, will be followed throughout the influenza season for both longer-term safety and vaccine protective efficacy.

On October 23, 2012, the sponsor stated in e-mail:

It is correct that we are not planning to administer the 125,000 doses early next year post-approval under a protocol (described in our response to Comment 7 of the September 28, 2012 IR submitted on October 15, 2012).

On November 9, 2012, CBER sent the following request to PSC:

Regarding your response to Comment 7 of our September 28, 2012, Information Request pertaining to your proposed Phase 4 study: As proposed in your May 8, 2008, submission to STN 125285 (Section 1.6.2.2.2), we recommend that you conduct the Phase 4 observational safety study in persons 18 years of age and older under a clinical protocol and recommend that this study be conducted as a Postmarketing Commitment (PMC). We recommend that you submit a study protocol and statistical analysis plan to CBER for review prior to initiating the study.

On November 26, 2012, PSC replied as follows:

We agree that an observational safety study is most effectively conducted as a post-authorization safety study under a protocol with pre-specified statistical analyses. To that end, we are in discussion with investigators at Kaiser-Permanente of Northern California, who are experienced in the conduct of such studies and who have access to very complete electronic health records for their large population of members.

The Kaiser-Permanente Health System begins immunizing for influenza in October (or earlier, if vaccine is available), so the earliest date that this study could be conducted is the 2013-14 season. The protocol with statistical analysis plan will be provided to CBER for review prior to initiating the study.

At this time, CBER has not received a protocol, statistical analysis plan, or proposal for a phase 4 general safety study in adults aged 18-49 years.

With regard to older adults, the sponsor has proposed a Phase 3/4 safety study (PSC11) to support accelerated and full approval in individuals 50 years of age and older. The primary objective is to evaluate the safety of Flublok with respect to the incidence and severity of common hypersensitivity reactions (rash, urticaria, swelling, and edema) occurring within 30 days after vaccination. The secondary objectives are (1) to compare the incidence and severity of common solicited local and systemic events occurring within 7 days after vaccination with Flublok or Fluzone, and (2) to compare the incidence and severity of all unsolicited adverse events occurring within 30 days after vaccination with Flublok or Fluzone. PSC has also proposed a Phase 3/4 study (PSC12) to evaluate protective efficacy of the vaccine, with a primary endpoint of laboratory-confirmed influenza-like illness. Secondary and additional endpoints pertaining to safety include serious adverse events, medically-attended adverse events, adverse events of interest (not specified), new-onset chronic illness, hospitalization, death, admission to an intensive care unit, pneumonia, mechanical ventilation, and absence from work.

At this time, CBER has not received a protocol, statistical analysis plan, or proposal for a phase 4 general safety study in adults aged 50 years and older.

7. Additional information (subsequent to BLA resubmission July 2012) related to pregnancy safety monitoring

Pregnancy registry: On September 21, 2012, the sponsor submitted a pregnancy registry proposal. On October 19, 2012, CBER sent an IR to PSC. On October 22, 2012, the sponsor responded and clarified that all pregnancies exposed to Flublok will be tracked, including those that begin within the first two months after vaccination; that pregnancies will be included regardless of the date of reporting; and that an “annual report” is a Periodic Safety Update Report. In addition, in response to CBER’s request to consider including maternal complications, PSC stated, “The Registry will collect significant obstetric complications, as indicated above....”

Study design and data collection: PSC has submitted its “Proposal for management of pregnancy registry.” According to the proposal, “This Registry will capture and follow all reported pregnancies to their conclusion and will additionally follows [sic] all live-born infants through their first well-baby check-up at 2-4 weeks of age.” The proposal states that the Patient Information Sheet will include contact information for women to report pregnancies. With the patient’s consent, the call center will obtain medical and demographic data. A follow-up form will be sent to the physician after the expected delivery date. Pregnancy outcomes (live births, spontaneous or elective abortions, and congenital defects) will be evaluated. The proposed analysis, copied verbatim from the sponsor’s submission, appears in italics below:

Specific monitoring criteria will be developed for evaluating signals, including:

- *Individual and composite data*
- *Use of the Rule of Three – i.e., that 3 exposure-specific cases with the same birth defect requires [sic] immediate evaluation, based on the statistical principle that the likelihood of observing 3 of any single defect in a cohort of 600 or fewer by chance alone is < 5%*
- *Primary analysis will include statistical considerations, power/relative risk calculation and probabilities associated with various birth defects using the March of Dimes database as a comparator.*

8. Recommendations

a. Routine pharmacovigilance

b. General safety study

A phase 4 general safety study should be conducted in adults aged 18-49 years. Access to healthcare claims will permit validation by medical record review [1]. This protocol-based study may use self-controlled or comparator approaches, and it should include a pre-specified statistical analysis plan.

c. Pregnancy registry

- i. Influenza vaccination is routinely recommended for pregnant women, but pregnancy was an exclusion criterion in the clinical trials. The general design of the proposed pregnancy registry has significant limitations, including potentially poor enrollment, high loss to follow up, and inability to test hypotheses. In addition, this registry design does not meet many of the desirable qualities described in the FDA guidance on pregnancy registries [2]. DE recommends using a design that is consistent with the FDA guidance [2]. The sponsor may also wish to consider the FDA’s Proposed Rule on Pregnancy and Lactation Labeling [3, 4].

- ii.** Elements of the registry should include the following:
1. The system should have an active recruitment plan. Many women may receive the vaccine in “non-traditional” settings, such as immunization clinics or pharmacies. Therefore, the vaccination may not be in the patient’s medical record or recorded in an automated healthcare database, and sole reliance on one of these sources may present difficulties in for recruitment and classification of exposures.
 2. Women should be enrolled in the registry prospectively, and any data from retrospective enrollments should be analyzed separately.
 3. The registry should include patient interviews (with both exposed and non-exposed individuals) that would allow the collection of detailed information, including information on confounding factors or risk modifiers that might be impossible to obtain by other means; family history of birth defects, smoking, alcohol, and exposures to over-the-counter medications
 4. The comparator group should consist, at a minimum, of a concurrent group of unexposed pregnant women matched for important covariates in relation to the exposed group.
 5. A plan should be developed for the extent and length of follow-up, and clinic and hospital charts should be available, so that outcomes can be confirmed. The protocol should specify *a priori* which pregnancy outcomes will be included and what fetal effects will be assessed. A published classification scheme for birth defects should be used.
 6. The statistical power of the registry to rule out or detect a difference in outcome based on sample size should be specified.

References

[1]

Postmarketing Studies and Clinical Trials – Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act.

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm>

[2]

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071639.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=Varicella%20pregnancy%20registry&utm_content=2

[3]

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093310.htm>

[4]

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>