Our STN: BL 125285/194

SUPPLEMENT APPROVAL
PMR FULFILLED LETTER

October 7, 2016

Protein Sciences Corporation
Attention: Penny L. Post, Ph.D.
1000 Research Parkway
Meriden, CT 06450-7159

Dear Dr. Post:

We have approved your request to supplement your Biologics License Application for Influenza Vaccine, Flublok®, to include a quadrivalent formulation (Flublok® Quadrivalent), for use in persons 18 years of age and older and to include data from the confirmatory clinical study to verify and describe the clinical benefit of Flublok (trivalent formulation) in persons 50 years of age and older.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT02290509 and NCT02285998.

FULFILLMENT OF POSTMARKETING REQUIREMENT FOR ACCELERATED APPROVAL

We approved Flublok (trivalent formulation) for use in persons 50 years of age and older on October 29, 2014, under the accelerated approval regulations with a post marketing requirement (PMR) (21 CFR 601.41) (STN: BL 125285/78). This submission contains the final report for the following PMR, listed in the October 29, 2014, supplement approval letter:

PMR #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.

We have completed the review of your submission and find that this requirement has been fulfilled.

MANUFACTURING

The final formulated Flublok Quadrivalent drug product will be filled, labeled, and packaged into single dose syringes at (b) (4) . The dating period for Flublok Quadrivalent shall be 6 months from the date of manufacture of final container vaccine, but not to exceed June 30th of the influenza season for which it was

formulated, when stored at 2-8°C (36-46°F). The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency.

LABELING

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to this BLA at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

Please submit an amendment to all pending supplemental applications for this BLA that include revised labeling incorporating a revised content of labeling that includes these changes.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for children less than 3 years of age for Flublok Quadrivalent because data from a randomized, controlled study demonstrated that children 6 months to less than 3 years of age showed diminished hemagglutinin inhibition (HI) antibody responses to Flublok (trivalent formulation) as compared to a U.S.-licensed influenza vaccine approved for use in this population, strongly suggesting that Flublok and Flublok Quadrivalent would not be effective in children younger than 3 years of age.

We are deferring submission of your pediatric studies for Flublok Quadrivalent for 3 years through 17 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of the approval of this BLA until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. This required study is listed below:

1. Deferred pediatric safety, immunogenicity and efficacy study (PSC17) in children 3 years through 17 years of age for active immunization for the prevention of disease caused by influenza virus subtypes A and types B contained in Flublok Quadrivalent.

   Final Study Protocol Submission Date: January 31, 2018

   Study Completion Date: June 30, 2019

   Final Report Submission Date: June 30, 2020

RELEASE/REPLACEMENT OF POSTMARKETING REQUIREMENT

Your Approval Letter of January 16, 2013, for Flublok (trivalent formulation) included the following pediatric postmarketing requirement:

2. Deferred pediatric safety, reactogenicity and immunogenicity 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 3 years through 5 years of age.

    Final Protocol Submission: June 30, 2015

    Study Completion Date: June 30, 2016

    Final Report Submission: June 30, 2017

Your Release from Postmarketing Requirement/New Postmarketing Requirement Letter of February 2, 2016, for Flublok (trivalent formulation) included the following pediatric postmarketing requirement:

2. Deferred pediatric study (PSC17) under PREA to evaluate the safety and effectiveness of a Flublok quadrivalent formulation in children 6 years through 17 years of age.

    Final Protocol Submission: January 31, 2018

    Study Completion Date: June 30, 2019

    Final Report Submission: December 31, 2019

We have determined that you are released from PMR study #2 from STN 125285/0 dated January 16, 2013, and from PMR study #2 from STN 125285/192 dated February 2, 2016, for the following reason:

We agree with your proposal discussed in the May 19, 2016, meeting (IND 15784) reporting on the pediatric PMR deferred studies #2 and #2 above to combine these studies into a single relative vaccine efficacy study in subjects 3 years through 17 years of age.

The above PMR deferred studies #2 and #2 will be replaced by the new pediatric PMR study #1 described above.

Submit the protocol to your IND (15784), with a cross-reference to this BLA (STN 125285) explaining that this protocol was submitted to the IND.

Submit final study reports to this BLA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated as:

- **Required Pediatric Assessment**

The status report for this study should include:

- the sequential number for the study as shown in this letter,
- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted), and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding this postmarketing study on our Web site http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIRMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your correspondence of September 26, 2016, as outlined below:

2. To provide the final report of the (b) (4) container closure integrity test method validation as performed by (b) (4).

   Final Report Submission: December 31, 2016

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125285.

Please use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study commitment as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Study Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;

- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

We will include information contained in the above-referenced supplement in your biologics license application file.

Sincerely yours,

Wellington Sun -S

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Wellington Sun, M.D.
Director Division of Vaccines and
Related Products Applications
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

Attachment: Approval Final Draft Labeling