DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

SUPPLEMENT APPROVAL LETTER
INCLUDING AN ACCELERATED APPROVAL

Our STN: BL **125408/127**

Seqirus, Inc.
Attention: Marva Schodel
350 Massachusetts Avenue
Cambridge, MA 02139

Dear Ms. Schodel:

Effective this date, we have approved your request to supplement your Biologics License Application (BLA) for Influenza Vaccine, to include a quadrivalent formulation (Flucelvax® Quadrivalent), for use in persons 4 years of age and older. For the age group 4 years to <18 years of age, we have approved your request to supplement your BLA for Influenza Vaccine according to the regulations for accelerated approval, 21 CFR 601.40-46.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT01992094 and NCT01992107.

ACCELERATED APPROVAL REQUIREMENTS

As requested in your letter of January 20, 2016, we are granting marketing approval of Flucelvax® Quadrivalent in persons 4 years to <18 years of age under the accelerated approval of biological products regulations, 21 CFR 601.40-46. Under these regulations we may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. This approval requires you to study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.

Approval under these regulations requires, among other things, that you conduct adequate and well-controlled studies to verify and describe clinical benefit attributable to this product. For this vaccine, clinical benefit in persons 4 years to <18 years will be confirmed by demonstration of efficacy against influenza disease.

Accelerated Approval Required Study

We remind you of your postmarketing requirement specified in your submissions of January 20, 2016 and April 7, 2016.

1. To conduct a study to evaluate the efficacy, safety and immunogenicity of the quadrivalent formulation of your Influenza Vaccine compared to a non-influenza comparator vaccine in persons 4 years to <18 years of age.

   Final Protocol Submission: September 30, 2016

   Study Completion: March 30, 2017

   Final Report Submission: August 30, 2018

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of April 7, 2016.

You must conduct the study with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by the quadrivalent formulation of your Influenza Vaccine in persons 4 to <18 years of age, or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43 (b), withdraw or modify approval if:

- A postmarketing clinical study fails to verify clinical benefit
- The applicant fails to perform the required postmarketing study with due diligence
- Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product
- The applicant fails to adhere to the postmarketing restrictions agreed upon
- The promotional materials are false or misleading
- Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

Submit final study reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing study requirement must be clearly designated as **Subpart E Postmarketing Study Requirements**.

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 FDA Form 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 titled, *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

PREGNANCY AND LACTATION LABELING RULE (PLLR)

Please note that you will need to submit labeling that conforms to the requirements of the final rule, *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling* by June 30, 2019.

PROMOTIONAL MATERIALS

Please note that the accelerated approval regulation concerning promotional materials (21 CFR 601.45) stipulates that all advertising and promotional labeling items that you wish to distribute in the first 120 days following approval, must have been received by FDA prior to the approval date. After approval, promotional items intended for dissemination after the first 120 days following approval must be submitted to the FDA 30 days prior to the anticipated distribution date. Please submit draft materials with a cover letter noting that the items are for accelerated approval, and an accompanying Form FDA 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)).

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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.

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. You should submit these reports to the Vaccine Adverse Event Reporting System (VAERS), For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at http://www.fda.gov/forindustry/electronicsubmissionsgateway/ucm387293.htm. For information on distribution reporting, please refer to the guidance for industry Electronic Submission of Lot Distribution Reports at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

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 ages 0 to 6 months of age because Flucelvax® Quadrivalent does not represent a meaningful therapeutic benefit over initiating vaccination at 6 months of age and is not likely to be used in a substantial number of infants < 6 months of age. Available data indicate that serum antibody responses to inactivated influenza vaccines in infants <6 months of age are not as robust as in older children due to inherent immaturity of the immune system and interference from maternal antibody.

We are deferring submission of your pediatric study for ages 6 months to <4 years of age for this application because the product is ready for approval for use in persons 4 years of age and older and the pediatric study in children 6 months to <4 years of age has not been completed.

Your deferred pediatric study required under 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 Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. This required study and timeline described in your letter of February 15, 2016, are listed below:

2. Deferred pediatric study (Study V130_10) under PREA to evaluate the safety and immunogenicity of your quadrivalent formulation of Influenza Vaccine in pediatric subjects 6 months to < 4 years of age.

   Final Protocol Submission: June 30, 2019

   Study Completion: August 30, 2020

   Final Report Submission: February 28, 2021

Submit the protocol to your IND 15744, with a cross-reference letter to this BLA STN 125408 explaining that this protocol was submitted to the IND.

Submit final study reports to this BLA STN 125408. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated as:

- **Required Pediatric Assessment**

We note that you have fulfilled the pediatric study requirement for ages 4 years to <18 years for this application.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your letters of August 18, 2015 and May 10, 2016 as outlined below:

3. To establish a pregnancy registry to prospectively collect data on spontaneously-reported exposures to Flucelvax® Quadrivalent or Flucelvax® during pregnancy and collect data on pregnancy outcomes. When the registry has enrolled a minimum of 600 evaluable subjects and collected data on the outcomes specified in the protocol, Seqirus will submit a full study report and continue enrolling in the registry pending CBER review and discussion of registry results with Seqirus.

   Final Protocol Submission: December 16, 2015

   Study Completion: August 31, 2020

   Final Report Submission: January 31, 2021

Please submit this clinical protocol to your IND 15744, with a cross-reference letter to this BLA STN 125408 explaining that this protocol was submitted to the IND.

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement. Supplements in support of labeling changes based on a postmarketing study report may be subject to a user fee. Please use the following designators to

prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. 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 this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each 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 these postmarketing studies on our Web site at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will include information contained in the above-referenced supplement in your Biologics License Application file.

Sincerely yours,

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: Approved Final Draft Labeling