DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

SUPPLEMENT ACCELERATED APPROVAL

Our STN: BL **125408/101**

Seqirus, Inc.
Attention: Marva Schodel
75 Sidney Ave.
Cambridge, MA 02139-4182

Dear Ms. Schodel:

Effective this date, we have approved your request to supplement your Biologics License Application (BLA) for Influenza Vaccine, to extend the age range for use of Flucelvax® to include persons 4 years to <18 years of age 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: NCT 00645411 and NCT01857206.

ACCELERATED APPROVAL REQUIREMENTS

As requested in your letter of January 20, 2016, we are granting marketing approval of Flucelvax® for use in persons 4 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 of age will be confirmed by demonstration of efficacy against influenza disease.

Accelerated Approval Required Study

We remind you of your post-marketing requirement specified in your submissions of January 20, 2016 and May 16, 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 May 16, 2016.

You must conduct the study with due diligence. If post-marketing studies fail to verify that clinical benefit is conferred by Influenza Vaccine in persons 4 years 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 post-marketing clinical study fails to verify clinical benefit
- The applicant fails to perform the required post-marketing study with due diligence
- Use after marketing demonstrates that post-marketing restrictions are inadequate to ensure safe use of the biological product
- The applicant fails to adhere to the post-marketing 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 post-marketing study requirement must be clearly designated as **Subpart E Post-marketing 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 —Post-marketing 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 because Flucelvax® 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 studies for ages 6 months to <4 years of age for this application because the product is ready for approval in persons 4 years to <18 years of age and the pediatric study in children 6 months to <4 years of age has not been initiated.

Fulfillment of Pediatric Post-marketing Requirement

Please note that this supplement contains the final study report for the following post-marketing requirement identified in the November 20, 2012 approval letter under STN 125408/0.

PMR #2 Deferred pediatric study (Study V58_31) under PREA to evaluate the safety of FLUCELVAX in children ages 4 years to < 18 years.

Final Protocol Submission: November 30, 2012

Study Completion Date: May 2014

Final Report Submission: November 2014

We have completed the review of your submission and find that you have fulfilled the pediatric study requirement for ages 4 years to <18 years for this application.

Release from Pediatric Post-marketing Requirement

We have completed the review of your submission and conclude that you are released from the following pediatric post-marketing requirement identified in the November 20, 2012 approval letter under STN 125408/0:

PMR #4 Deferred pediatric study (Study V58_35) under PREA to evaluate the safety and immunogenicity of FLUCELVAX in children ages 6 months to < 4 years.

Final Protocol Submission: August 31, 2016

Study Completion Date: May 2018

Final Report Submission: November 2018

We have reviewed your submission and have determined that you are released from the above post-marketing requirement for the following reason:

You will conduct studies in infants and children 6 months to <4 years of age using your quadrivalent formulation of Influenza Vaccine.

The above pediatric post-marketing requirement is now considered closed and will be replaced by the new post-marketing requirement described below.

New Pediatric Post-marketing Requirement

Your deferred pediatric studies required under 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required post-marketing studies. The status of these post-marketing studies 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 post-marketing commitments or required studies or clinical trials. This required study is 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 Date: 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 post-marketing study must be clearly designated as:

- **Required Pediatric Assessment**

For each post-marketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on post-marketing studies for this product. Label your annual report as an **Annual Status Report of Post-marketing 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 post-marketing 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 post-marketing 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