Our STN: BL 125692/0

BLA APPROVAL
INCLUDING AN ACCELERATED APPROVAL

Seqirus, Inc.
Attention: Sonja B. Loar, Pharm. D.
50 Hampshire Street
9th Floor
Cambridge, MA 02139

January 31, 2020

Dear Dr. Loar:

Please refer to your Biologics License Application (BLA) submitted on January 31, 2019, and received on February 1, 2019, under section 351(a) of the Public Health Service Act (PHS Act) for Influenza A (H5N1) Monovalent Vaccine, Adjuvanted.

LICENSING

We have approved your BLA for Influenza A (H5N1) Monovalent Vaccine, Adjuvanted effective this date for use in persons 6 months of age and older. For use in persons 6 months through 17 years of age, we have approved your BLA according to the regulations for accelerated approval, 21 CFR 601.41.

You are hereby authorized to introduce or deliver for introduction into interstate commerce, Influenza A (H5N1) Monovalent Vaccine, Adjuvanted under your existing Department of Health and Human Services U.S. License No. 2049. However, we acknowledge the statement in your submission of January 29, 2020, that Seqirus, Inc. does not intend to market this product for commercial distribution in the U.S. since it will be produced and distributed under contract to the U.S. Government as part of national pandemic preparedness initiatives. In addition, we acknowledge that you intend to collaborate with the Food and Drug Administration (FDA) and other governmental agencies in the U.S. on plans to collect additional safety and effectiveness data in the U.S., when Influenza A (H5N1) Monovalent Vaccine, Adjuvanted is used. Furthermore, if Influenza A (H5N1) Monovalent Vaccine, Adjuvanted is used in another country and additional safety and effectiveness data are obtained, you will provide these data to the FDA.

Influenza A (H5N1) Monovalent Vaccine, Adjuvanted is indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is approved for use in persons 6 months of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT00812019, NCT01776541, NCT01766921, NCT01776554 and NCT02839330.

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval 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 clinical trials to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as demonstration of effectiveness of Flucelvax Quadrivalent in persons 6 months through 17 years of age.

Accelerated Approval Required Studies

We remind you of your postmarketing requirements specified in your submission of January 29, 2020:

1. To conduct a study (V130_12) to evaluate the efficacy, safety and immunogenicity of Flucelvax Quadrivalent compared to a non-influenza comparator vaccine in persons 4 years to <18 years of age.

   Final Protocol Submission: December 13, 2018

   Study Completion: September 30, 2019

   Final Report Submission: July 31, 2020

2. To conduct a study (Study V130_10) to evaluate the safety and immunogenicity of Flucelvax Quadrivalent 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

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of January 29, 2020.

You must conduct these studies with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by Influenza A (H5N1) Monovalent Vaccine, Adjuvanted, 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.

Your accelerated approval postmarketing required studies are 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.

Please submit final study reports as supplements to this BLA 125692. For administrative purposes, all submissions related to these postmarketing study requirements must be clearly designated as “Subpart E Postmarketing Study Requirements.”

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Influenza A (H5N1) Monovalent Vaccine, Adjuvanted at your facility located at Holly Springs, North Carolina. You may label your product with the proprietary name AUDENZ and market it as a single-dose pre-filled syringe.

ADVISORY COMMITTEE

We did not refer your application to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for Influenza A (H5N1) Monovalent Vaccine, Adjuvanted shall be 12 months from the date of manufacture when stored at 2 °C to 8 °C. The date of manufacture shall be defined as the date of initiation of final fill of the formulated drug product into final containers. The dating period for storage of the (b) (4) monovalent virus antigen drug substance shall be (b) (4) months when stored at (b) (4) .

FDA LOT RELEASE

Please submit final formulated bulk samples of the product together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, 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

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Influenza A (H5N1) Monovalent Vaccine, Adjuvanted, or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling submitted under Amendment 48, dated January 30, 2020, and the draft carton and container labeling submitted under Amendments 46 and 43, dated January 29, 2020, and January 17, 2020, respectively.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (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.

The SPL will be accessible via publicly available labeling repositories.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels that are identical to the package and container labels submitted on January 17, 2020 and January 29, 2020, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications

All final labeling should be submitted as Product Correspondence to this BLA 125692 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

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 at least 30 days prior to the anticipated distribution date. Since, as stated in your January 29, 2020, submission, you do not intend to market this product for commercial distribution, we understand that you will not be distributing promotional advertising or promotional labeling materials. However, should you develop any advertising and/or promotional labeling related to this product (for example, educational brochures), 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 *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-and-non-electronic-format-promotional-labeling-and-advertising-materials-for-human-prescription-drugs.

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)).

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. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports . 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.

For information on the postmarketing safety reporting requirements for combination products as described in 21 CFR 4, Subpart B, and the dates by which combination product applicants must comply with these requirements, please refer to the Postmarketing Safety Reporting for Combination Products webpage available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

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 deferring submission of your pediatric study for infants and children 0 to < 6 months of age for this application, because this product is ready for approval for use in individuals 6 months of age and older and the pediatric study has 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 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 is listed below:

3. Deferred pediatric study V89_19 under PREA to evaluate the safety and immunogenicity of AUDENZ when administered to healthy infants 0 to < 6 months of age.

   Final Protocol Submission: 60 days after notification by the FDA to finalize the protocol, which will be related to an imminent H5N1 influenza virus pandemic (sustained human to human H5N1 transmission)

   Study Completion Date: 24 months after initiation of the study

   Final Report Submission: 8 months after completion of data collection

Submit the protocol to your IND 13536, with a cross-reference letter to this BLA 125692 explaining that this protocol was submitted to the IND.

Submit final study reports to this BLA 125692. 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 6 months through 17 years for this application.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your letter of November 20, 2019, as outlined below:

4. To establish a pregnancy registry in the U.S. that is able to prospectively collect data on an actively recruited cohort to study the safety of Audenz Vaccine during pregnancy. A draft protocol for this pregnancy registry will be prepared under the assumption that the vaccine would be distributed to the general population in the U.S. in an officially-declared H5N1 influenza virus pandemic. Once the circumstances of vaccine usage in an officially-declared H5N1 influenza virus pandemic are determined by the U.S. Government, Seqirus will work with the FDA, in coordination with BARDA (Biomedical Advanced Researh and Development Authority) and CDC (Center for Disease Control), to finalize the protocol and initiate the registry.

   Draft Protocol Submission: December 31, 2020

   Final Protocol Submission: 90 days after notification by the FDA

   Initiate Registry: 60 days after notification by FDA

   Study Completion Date: 24 months after initiation of the registry

   Final Report Submission: 12 months after completion of data collection

Please submit clinical protocols to your IND 13536, and a cross-reference letter to this BLA 125692 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. 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 website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Marion F. Gruber, Ph.D.
Director
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research