DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BL **125510/0** **ACCELERATED APPROVAL**

Novartis Vaccines and Diagnostics, Inc.
Attention: Mayuresh Gadre
350 Massachusetts Avenue
Cambridge, MA 02139

Dear Mr. Gadre:

Effective this date, we have approved your biologics license application (BLA) for Influenza Vaccine, Adjuvanted, according to the regulations for accelerated approval, 21 CFR 601.40-46. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Influenza Vaccine, Adjuvanted under your existing Department of Health and Human Services U.S. License No. 1751. Influenza Vaccine, Adjuvanted is indicated for active immunization against disease caused by influenza subtypes A and type B contained in the vaccine. Influenza Vaccine, Adjuvanted is approved for use in persons 65 years of age and older.

The review of this product was associated with the following National Clinical Trial (NCT) number: NCT01162122.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Influenza Vaccine, Adjuvanted. The influenza antigen drug substance will be manufactured at Novartis Vaccines and Diagnostics LTD in [redacted]. The final formulated product consisting of the influenza antigen drug substance and MF59C.1 adjuvant will be manufactured, filled, labeled, and packaged at Novartis Vaccines and Diagnostics [redacted]. You may label your product with the proprietary name Fluad and will market it in prefilled syringes containing a single dose of vaccine.

DATING PERIOD

The dating period for Influenza 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 drug product formulation.

FDA LOT RELEASE

Please submit samples from formulated trivalent bulk with MF59C.1 adjuvant 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).

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 Vaccine, Adjuvanted, or in the manufacturing facilities.

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, packing, 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

ACCELERATED APPROVAL

We are granting marketing approval of this product 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 will be confirmed in adults 65 years of age and older by demonstration of efficacy against influenza disease.

ACCELERATED APPROVAL REQUIRED TRIAL

We remind you of your postmarketing requirements specified in your submission of November 4, 2015.

1. To conduct the confirmatory trial (V118_18) to assess the efficacy of Fluad aQIV (MF59C.1 adjuvanted quadrivalent inactivated seasonal influenza vaccine) as compared to an active

control, Tdap (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Boostrix)), in adults 65 years of age and older.

Final Protocol Submission: September 2015

Study Completion Date: November 2018

Final Report Submission: August 2019

We expect you to complete and report this study within the framework described in your letter of November 4, 2015.

You must conduct the trial with due diligence. If the postmarketing trial fails to verify that clinical benefit is conferred by Influenza Vaccine, Adjuvanted, or is 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 trial fails to verify clinical benefit
- The applicant fails to perform the required postmarketing trial 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 the final trial report to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing trial requirement must be clearly designated as **Subpart E Postmarketing Study Requirements**.

Please provide your final content of labeling in Structured Product Labeling (SPL). In addition, please submit three original paper copies of 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, *SPL Standard for Content of Labeling Technical Qs and As*, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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)).

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 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/PostMarketActivities/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 children 9 to less than 17 years of age for this application because use of the biological product in this age group does not represent a meaningful therapeutic benefit over existing influenza vaccines and the product is not likely to be used in a substantial number of pediatric patients in this group.

We are deferring submission of your pediatric studies for children 0 to less than 9 years of age because this product is ready for approval for use in adults 65 years of age and older and the pediatric studies have not been completed.

Your deferred pediatric studies required under 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below:

2. Deferred pediatric trial (V118_05) under PREA to evaluate the efficacy, safety and immunogenicity of Fluad (aQIV) when administered to children 6 months to less than 72 months of age.

   Final Protocol Submission: August 2013

   Study Completion Date: July 2018

   Final Report Submission: April 2019

3. Deferred pediatric trial (V70_29) under PREA to evaluate the safety and immunogenicity of Fluad when administered to children 6 months to less than 72 months of age.

   Final Protocol Submission: July 2011

   Study Completion Date: July 2012

   Final Report Submission: April 2019

4. Deferred pediatric trial (V118_19) under PREA to evaluate the safety and immunogenicity of Fluad (aQIV) when administered to children 6 years to less than 9 years of age.

   Final Protocol Submission: September 2020

   Study Completion Date: May 2022

   Final Report Submission: February 2023

5. Deferred pediatric trial (V118_14) under PREA to evaluate the safety and immunogenicity of Fluad (aQIV) when administered to infants less than 6 months of age.

   Final Protocol Submission: September 2020

   Study Completion Date: May 2022

   Final Report Submission: February 2023

Submit clinical protocols to your IND [redacted], with a cross-referencing letter to this BLA STN BL 125510 explaining that these protocols were submitted to the IND.

Submit final study reports to this BLA STN BL 125510. If the information in the final study report supports a change in the labeling, the final study report should be submitted as a supplement. We may also request a supplement if we think labeling changes are needed. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated **Required Pediatric Assessment(s).**

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

- **Postmarketing Study Requirement - Correspondence**
- **Postmarketing Study Requirement - Final Study Report**
- **Supplement contains Postmarketing Study Requirement – 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 an **Annual Status Report of Postmarketing Study 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 requirement should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original schedule for the requirement;
- the status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and
- an explanation of the status of the requirement including, 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 trials on our website (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInforamtion/Post-marketingPhaseIVCommitments/default.htm).

PREGNANCY AND LACTATION LABELING RULE (PLLR)

Please note that you will need to submit labeling that conforms to the format and content requirements of the "Pregnancy and Lactation Labeling Rule" by no later than 4 years after June 30, 2015.

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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments.

Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Sincerely,

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

Attachment: Approved Final Draft Labeling