Our STN: BL 125775/0

BLA APPROVAL
May 23, 2023

GlaxoSmithKline Biologicals
Attention: Steven A. Rubin, Ph.D.
14200 Shady Grove Road
Rockville, MD 20850

Dear Dr. Rubin:

Please refer to your Biologics License Application (BLA) received September 2, 2022, submitted under section 351(a) of the Public Health Service Act (PHS Act) for Respiratory Syncytial Virus Vaccine, Adjuvanted.

We also refer to our approval letter dated May 3, 2023, which contained the following error:

> The dating period for the $AS01_E$ adjuvant suspension component of Respiratory Syncytial Virus Vaccine, Adjuvanted was incorrectly described as 24 months in this statement:
>
> The dating period for the RSVPreF3 antigen component and the $AS01_E$ adjuvant suspension component of Respiratory Syncytial Virus Vaccine, Adjuvanted shall be 24 months from the date of manufacture when stored at 2ºC to 8ºC.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain May 3, 2023, the date of the original approval letter.

LICENSING

We have approved your BLA for Respiratory Syncytial Virus Vaccine, Adjuvanted effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Respiratory Syncytial Virus Vaccine, Adjuvanted under your existing Department of Health and Human Services U.S. License No. 1617. Respiratory Syncytial Virus Vaccine, Adjuvanted is indicated for active immunization for the prevention of lower respiratory tract disease caused by respiratory syncytial virus in individuals 60 years of age and older.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT04886596, NCT03814590, NCT04732871, NCT04841577, NCT05059301, and NCT04657198.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Respiratory Syncytial Virus Vaccine, Adjuvanted. You may label your product with the proprietary name AREXVY.

The lyophilized respiratory syncytial virus glycoprotein F stabilized in pre-fusion conformation (RSVPreF3) antigen component of the vaccine will be manufactured, filled, and lyophilized at GSK Biologicals (b) (4) , Belgium. The AS01$_E$ adjuvant suspension component of the vaccine will be manufactured and filled at GSK Biologicals (b) (4) , Belgium and GSK Vaccines (b) (4) . The lyophilized antigen component, the adjuvant suspension component and the final product AREXVY will be labeled and packaged at GSK Biologicals (b) (4) , Belgium, GSK Vaccines (b) (4) GlaxoSmithKline Vaccines, (b) (4)

The vaccine will be supplied in a ten dose configuration that contains ten single-dose vials of lyophilized antigen component and ten single-dose vials of adjuvant suspension component.

DATING PERIOD

The dating period for the RSVPreF3 antigen drug substance shall be (b) (4) months when stored at (b) (4) The dating period for the RSVPreF3 antigen component of Respiratory Syncytial Virus Vaccine, Adjuvanted shall be 24 months from the date of manufacture when stored at 2ºC to 8ºC. The dating period for the AS01$_E$ adjuvant suspension component of Respiratory Syncytial Virus Vaccine, Adjuvanted shall be 36 months from the date of manufacture when stored at 2ºC to 8ºC. The dates of manufacture of the RSVPreF3 antigen and AS01E adjuvant suspension components shall be defined as the dates of filling into final containers. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency. The expiration date for the packaged product, lyophilized antigen component and adjuvant suspension component, shall be dependent on the shortest expiration date of any component.

COMPARABILITY PROTOCOL

This approval also includes comparability protocols for the replacement of reference standards, internal controls, and key reagents as identified below.

For the RSVPreF3 antigen component:

(b) (4)

(b) (4)

For the AS01$_E$ adjuvant component:

(b) (4)

Under 21 CFR 601.12(e), approval of a comparability protocol may justify a reduced reporting category for a particular change. In your annual report (21 CFR 601.12(d)), you should report information confirming that the change(s) meet(s) the requirements specified in your approved comparability protocol. Include the information described in 21 CFR 601.12(d)(3).

Please report qualifying information on an internal control or reference standard batch as a **Supplement – Changes Being Effected in 30 Days** (21 CFR 601.12(c)) following agreement with CBER and in limited situations when a batch does not fully meet the acceptance criteria in the comparability protocol and there is a limited supply of the approved batch. You should include the information described in 21 CFR 601.12 (b)(3) in this supplement. Although you may distribute the product made using this change 30

days after FDA receives the supplement, continued distribution of the product made with the change will be subject to our final approval of the supplement.

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. Please submit 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, electronically through the Electronic Submission Biological Product Deviation Report (eBPDR) web application or at the address below. Links for the instructions on completing the electronic form eBPDR may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations: eBPDR may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations:

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 Respiratory Syncytial Virus Vaccine, Adjuvanted, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including the Package Insert submitted under amendment 47, dated May 2, 2023, the draft carton label submitted under

amendment 43, dated April 24, 2023, and the draft container labels submitted under amendment 40, dated April 19, 2023.

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. Content of labeling must be identical to the Package Insert submitted on May 2, 2023. 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.

CARTON AND CONTAINER LABELS

Please electronically submit a final printed carton label identical to the carton label submitted on April 24, 2023, and container labels identical to the container labels submitted on April 19, 2023, 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/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

All final labeling should be submitted as Product Correspondence to this BLA STN BL 125775 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with 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 advertising 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). In addition to the reporting requirements in 21 CFR 600.80, you must submit adverse experience reports for Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), and supraventricular arrhythmia as 15-day expedited reports to the Vaccine Adverse Event Reporting System (VAERS). GBS, ADEM, and supraventricular arrhythmia reports must be submitted as 15-day expedited reports for 3 years following the date of product licensure. 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-vaccines. 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 2 years because there is evidence strongly suggesting that the biological product would be unsafe in this pediatric group.

We are deferring submission of your pediatric studies for ages 2 to 18 years 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 studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these

postmarketing studies must be reported according to 21 CFR 601.28 and section 505B(a)(4)(C) 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. These required studies are listed below:

1. Deferred pediatric study under PREA (Study RSV OA=ADJ-015) to evaluate the safety and effectiveness in children and adolescents 2 to 18 years of age.

   Final Protocol Submission: January 31, 2024

   Study Completion Date: April 14, 2026

   Final Report Submission: May 30, 2026

2. Deferred pediatric study under PREA (Study RSV OA=ADJ-016) to evaluate the safety and effectiveness in children and adolescents 2 to 18 years of age.

   Final Protocol Submission: January 31, 2026

   Study Completion Date: April 18, 2028

   Final Report Submission: May 30, 2028

Submit the protocols to your IND 18540 with a cross-reference letter to this BLA STN BL 125775 explaining that these protocols were submitted to the IND.

Submit final study reports to this BLA STN BL 125775. In order for your PREA PMRs to be considered fulfilled, you must submit and receive approval of either an efficacy or a labeling supplement. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated as:

- **Required Pediatric Assessment(s)**

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risks of GBS and ADEM.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following study:

3. EPI-RSV-041 VS US DB (220149), a postmarketing active surveillance study, to evaluate Guillain-Barré syndrome (GBS) and acute disseminated encephalomyelitis (ADEM) in adults 60 years and older vaccinated with AREXVY in the United States. Using a self-controlled risk interval (SCRI) design, the study will be conducted in the Sentinel System, and evaluate 1.9 million individuals vaccinated with AREXVY.

   We acknowledge the timetable you submitted on April 17, 2023, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: June 30, 2024

   Study Completion Date: June 30, 2030

   Final Report Submission: December 31, 2031

Please submit the protocol to your IND 18540 with a cross-reference letter to this BLA STN BL 125775 explaining that this protocol was submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit the final study report to the BLA. If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement to this BLA STN BL 125775. For administrative purposes, all submissions related to this postmarketing study required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. 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.

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 requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, 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 studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your letter of April 20, 2023, as outlined below:

4. EPI-RSV-041 VS US DB (220149), a postmarketing active surveillance study, to evaluate atrial fibrillation in adults 60 years and older vaccinated with AREXVY in the United States. Using a self-controlled risk interval (SCRI) design, the study will be conducted in the Sentinel System.

Final Protocol Submission: June 30, 2024

Study Completion Date: June 30, 2030

Final Report Submission: December 31, 2031

Please submit the clinical protocol to your IND 18540 and a cross-reference letter to this BLA STN BL 125775 explaining that this protocol was submitted to the IND.

If the information in the final study report supports a change in the label, 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 Managers for this application.

Sincerely,

David C. Kaslow, MD
Director
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research