Our STN: BL 125814/0

BLA APPROVAL AND ACCELERATED BLA APPROVAL

Merck Sharp & Dohme LLC
Attention: Donna Zacholski
P.O. Box 1000
UG2D-68
North Wales, PA 19454-2505

June 17, 2024

Dear Ms. Zacholski:

Please refer to your Biologics License Application (BLA) received on October 18, 2023, submitted under section 351(a) of the Public Health Service Act (PHS Act) for Pneumococcal 21-valent Conjugate Vaccine.

LICENSING

We have approved your BLA for Pneumococcal 21-valent Conjugate Vaccine effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Pneumococcal 21-valent Conjugate Vaccine under your existing Department of Health and Human Services U.S. License No. 0002. Pneumococcal 21-valent Conjugate Vaccine is indicated for active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older.

Effective this date, we have also approved your BLA for Pneumococcal 21-valent Conjugate Vaccine, under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and the regulations for accelerated approval, 21 CFR 601.41. Merck Sharp & Dohme LLC is hereby authorized to introduce or deliver for introduction into interstate commerce, Pneumococcal 21-valent Conjugate Vaccine under their existing Department of Health and Human Services U.S. License No. 0002. Pneumococcal 21-valent Conjugate Vaccine is indicated for active immunization for the prevention of pneumonia caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older.

You may label your product with the proprietary name CAPVAXIVE and market it in 0.5 mL doses within 1.5-mL single-dose prefilled Luer Lock syringes with tip caps. The vaccine will be supplied in cartons of 1 or 10 syringes.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT04168190, NCT05425732, NCT05464420, NCT05526716, and NCT05420961.

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval statutory provisions and regulations, we may grant marketing approval for a biological product on the basis of adequate and well-controlled studies 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 statutory provisions and regulations requires, among other things, that you conduct adequate and well-controlled studies to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as prevention of pneumococcal pneumonia caused by the serotypes in CAPVAXIVE.

Accelerated Approval Required Study

We remind you of your postmarketing requirement specified in your submissions of, February 14, 2024, and May 30, 2024.

1. To conduct an observational hybrid study using both primary and secondary data collection with a test-negative case-control design with the objective of assessing the effectiveness of CAPVAXIVE in preventing hospitalized, confirmed community acquired pneumonia (CAP, invasive and non-invasive) caused by *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals ≥65 years of age. The clinical protocol (V116-011-00) is entitled “A Test-Negative Case-Control Study to Evaluate the Effectiveness of V116 Against Pneumococcal Pneumonia in Older Adults.”

   Serotype-Specific Urinary Antigen Detection (SSUAD) and Pneumococcal Antigen Detection (PAD) assays validation protocols submission: November 1, 2024

   SSUAD and PAD validation reports submission: May 30, 2025

   Final Clinical Protocol Submission: May 30, 2025

   Final Study Implementation Readiness Verification Submission: June 16, 2025

   Study Initiation: June 30, 2025

   Study Completion: June 29, 2029

Final Report Submission: December 31, 2029

We expect you to complete design, implementation readiness verification, initiation, accrual, completion, and reporting of these studies within the framework described in your communications of February 9, 2024, February 14, 2024, and May 30, 2024.

Please submit the clinical protocol, assay validation protocols, and validation reports, to your IND 19316, with a cross-reference letter to this BLA, STN BL 125814, explaining that this information was submitted to the IND. Please refer to the sequential number for each study and the submission number as shown in this letter.

You must conduct this study with due diligence. If required postmarketing studies fail to verify that clinical benefit is conferred by Pneumococcal 21-valent Conjugate Vaccine, or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval.

You must submit reports of the progress of each study listed above as required under section 506(c) of the FDCA to this BLA 180 days after the date of approval of this BLA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under 506(c) of the FDCA. The initial report will be a standalone submission and the subsequent report will be combined with your application's postmarketing annual status report required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval. Submit the subsequent 180-day report with your application's postmarketing annual status report. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.

Your 180-day report must include the information listed in 21 CFR 601.70(b). FDA recommends that you use form FDA 3989 PMR/PMC Annual Status Report for Drugs and Biologics, to submit your 180-day reports. Form FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

Your 180-day reports, including both the standalone 180-day report submitted 180 days after the date of approval and the 180-day report submitted with your postmarketing annual status report, must be clearly designated as **180-Day AA PMR Progress Report.**

FDA will consider the submission of your postmarketing annual status report under section 506B(a)(1) of the FDCA and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year, to satisfy the periodic reporting requirement under section 506B(a)(2) of the FDCA. You are also required to submit information related to your confirmatory study as part of your annual postmarketing reporting requirement under section 506B(a)(1) of the FDCA until the FDA notifies you,

in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information. 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 Postmarketing Requirements and 506B Commitments are fulfilled or released.

Please submit the final study report as a supplement to this BLA, STN BL 125814. For administrative purposes, all submissions related to this postmarketing study requirement must be clearly designated as "**Subpart E Postmarketing Study Requirements**."

Accelerated Approval 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. Please submit draft materials with a cover letter noting the items that 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 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)).

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/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Pneumococcal 21-valent Conjugate Vaccine drug substance at Merck Sharp and Dohme LLC, (b) (4) Drug product is formulated and filled at (b) (4) . The finished product is labeled and packaged at Merck Sharp and Dohme LLC, (b) (4) ; and Merck Sharp & Dohme LLC, (b) (4) .

ADVISORY COMMITTEE

We did not refer your application to the Vaccines and Related Biological Products Advisory Committee 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 Pneumococcal 21-valent Conjugate Vaccine shall be 18 months from the date of manufacture when stored at 2–8°C. The date of manufacture shall be defined as the date of (b) (4) . Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency.

COMPARABILITY PROTOCOLS

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 changes meet the requirements specified in your approved comparability protocols for introduction of new DP secondary reference standards and shelf-life extension of secondary reference standards and for introduction of new Drug Substance reference standards used to determine (b) (4) and shelf-life extension of the DS reference standards. Include the information described in 21 CFR 601.12(d)(3).

You should report information confirming that the changes meet the requirements specified in your approved comparability protocol for introduction of new Drug Product primary reference standards as a **Supplement – Changes Being Effected in 30 Days** (21 CFR 601.12(c)). 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. 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 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 :

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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 Pneumococcal 21-valent Conjugate Vaccine, or in the manufacturing facilities.

LABELING

Under 21 CFR 201.57(c)(18), patient labeling must be referenced in section 17 PATIENT COUNSELING INFORMATION. Patient labeling must be available and may either be reprinted immediately following the full prescribing information of the package insert or accompany the prescription product labeling.

We hereby approve the draft content of labeling including Package Insert and Patient Package Insert submitted under amendment 37, dated June 12, 2024, and the draft package and container labels submitted under amendment 23, dated April 11, 2024.

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 and Patient Package Insert submitted on June 12, 2024. 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 identical to the package and container labels submitted on April 11, 2024, 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 125814 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) 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.

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 waiving the pediatric study requirement for the pneumonia indication because the necessary studies are impossible or highly impracticable. The routine use of pneumococcal conjugate vaccines (PCVs) in infants has resulted in a decreased prevalence of pneumococcal disease (PD) in the pediatric population. An active-controlled comparator clinical efficacy trial would require a sample size considered prohibitively large. In addition, there are currently no reliable methods for detecting vaccine-type nonbacteremic pneumonia in children.

We are waiving the pediatric study requirement for the invasive pneumococcal disease (IPD) indication for ages 0 to <2 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group. PCVs currently approved for use in the pediatric population are designed to

protect against the serotypes prevalent in infant disease in the pre-vaccine era. Furthermore, the incidence of disease due to serotypes in CAPVAXIVE accounts for a very small number of cases in children <5 years. In addition, due to limitations of the neonatal immune response, initiating vaccination at 0 to <6 weeks of age with CAPVAXIVE would not provide a meaningful therapeutic benefit over initiating vaccination with other licensed PCVs at 6 weeks of age.

We are deferring submission of your pediatric study for ages 2 to <18 years for the IPD indication because this product is ready for approval for use in adults 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)(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. This required study is listed below:

2. Deferred pediatric study under PREA to evaluate the safety and immunogenicity of CAPVAXIVE in pediatric patients ages 2 to <18 years.

   Final Protocol Submission: July 31, 2024

   Study Completion Date: June 30, 2026

   Final Report Submission: December 31, 2026

Submit the protocol to your IND 19316, with a cross-reference letter to this BLA, STN BL 125814 explaining that this protocol was submitted to the IND.

Submit the final study report to this BLA STN BL125814. For your PREA PMR 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 this required pediatric postmarketing study must be clearly designated as:

- **Required Pediatric Assessment(s)**

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