Our STN: BL 125731/0

BLA APPROVAL AND
BLA ACCELERATED APPROVAL

Wyeth Pharmaceuticals LLC
Attention: Patrick Thomas
500 Arcola Road
G4450
Collegeville, PA 19426

June 10, 2021

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) submitted and received October 8, 2020, under section 351(a) of the Public Health Service Act (PHS Act) for Pneumococcal 20-valent Conjugate Vaccine.

We also refer to our approval letter dated June 8, 2021, which contained the following error:

> The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain June 8, 2021, the date of the original approval letter.

LICENSING

We have approved your BLA for Pneumococcal 20-valent Conjugate Vaccine effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Pneumococcal 20-valent Conjugate Vaccine under your existing Department of Health and Human Services U.S. License No.0003. Pneumococcal 20-valent Conjugate Vaccine (Prevnar 20) is indicated for active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older and the prevention of pneumonia caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in adults 18 years of age and older.

Effective this date, we have also approved your BLA for Pneumococcal 20-valent Conjugate Vaccine, according to the regulations for accelerated approval, 21 CFR 601.41. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Pneumococcal 20-valent Conjugate Vaccine under your existing Department of Health and Human Services U.S. License No. 0003. Pneumococcal 20-valent Conjugate Vaccine is indicated for active immunization for the prevention of pneumonia caused by *Streptococcus pneumoniae* serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F in adults 18 years of age and older.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT02955160, NCT03642847, NCT03313037, NCT03760146, NCT03828617 and NCT03835975.

ACCELERATED APPROVAL REQUIREMENTS

Under accelerated approval regulations (21 CFR 601.41), 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 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 7 new serotypes in Prevnar 20 (8, 10A, 11A, 12F, 15B, and 33F).

Accelerated Approval Required Studies

We remind you of your postmarketing requirement specified in your submission of May 5, 2021.

1. To conduct a study to assess the effectiveness of Prevnar 20 in adults ≥ 65 years of age in preventing community acquired pneumococcal pneumonia caused by pneumococcal serotypes 8, 10A, 11A, 12F, 15B 22F and 33F in the vaccine. The original protocol for this study entitled “A Phase 4 Study Using a Test-Negative Design to Evaluate the Effectiveness of a 20-valent Pneumococcal Conjugate Vaccine Against Vaccine-Type Radiologically-Confirmed Community Acquired Pneumonia in Adults ≥ 65 years of age” (Study B7471015) was submitted on January 15, 2021.

Final Protocol Submission:	August 31, 2021
Study Completion:	May 31, 2027
Final Report Submission:	November 30, 2027

We expect you to complete design, initiation, accrual, completion, and reporting of these studies within the framework described in your letter of May 20, 2021.

You must conduct this study with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by Pneumococcal 20-valent Conjugate Vaccine, 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.

Please submit the protocol to your IND 17039, with a cross-reference letter to this BLA, STN BL 125731 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.

Your accelerated approval postmarketing required study is 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 the final study report as a supplement to this BLA, STN BL 125731. 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 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/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)).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Pneumococcal 20-valent Conjugate Vaccine pneumococcal polysaccharide Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F at Wyeth (b) (4) CRM197 protein and pneumococcal polysaccharide Serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F at Wyeth (b) (4) polysaccharide-CRM197 conjugate Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F at Pfizer (b) (4) and polysaccharide-CRM197 conjugate Serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F at Wyeth (b) (4) The final formulated product will be manufactured, filled, and primary packaged at Pfizer (b) (4), and labeled and secondary packaged at Pfizer Manufacturing (b) (4).

You may label your product with the proprietary name PREVNAR 20 and market it in 1 mL glass syringe with a Luer lock closure with 0.5 mL dose of vaccine.

We did not refer your application to the Vaccines and Related Biological Product 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 Pneumococcal 20-valent Conjugate Vaccine shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date filling is initiated of the formulated drug product. Following the final sterile filtration, no reprocessing/reworking is allowed without prior approval from the Agency.

COMPARABILITY PROTOCOL

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 protocol. Include the information described in 21 CFR 601.12(d)(3).

FDA LOT RELEASE

Please submit final container samples of the product and each kit component 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, 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 Pneumococcal 20-valent Conjugate Vaccine, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert submitted under amendment 44, dated June 8, 2021 and the draft carton and container labels submitted under amendment 39, dated June 1, 2021.

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 [choose all that apply: Package Insert, Patient Package Insert, Instructions for Use, and Medication Guide] submitted on [DATE]. 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 final printed carton and container labels identical to the carton submitted and the container label submitted on June 1, 2021, 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 125731 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), 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/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 weeks for the invasive pneumococcal disease indication, 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.

We are waiving the pediatric study requirement for this application in children 0 through 17 years of age for the pneumonia indication, because necessary studies are impossible or highly impracticable.
We are deferring submission of your pediatric studies for ages 6 weeks through 17 years in this application for the invasive pneumococcal disease indication, because this product is ready for approval for use in adults before all pediatric studies have 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 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 under section 506B of the FDCA are released or fulfilled. These required studies are listed below:

2. Deferred pediatric study (B7471011) under PREA to evaluate the safety and immunogenicity of the 2, 4, 6, and 12-month schedule of Prevnar 20 in infants and toddlers 6 weeks through 12 months of age in the United States (U.S.).

   Final Protocol Submission: May 8, 2020

   Study Completion Date: August 31, 2022

   Final Report Submission: December 31, 2022

3. Deferred pediatric study (B7471013) under PREA to evaluate the safety of the 2, 4, 6, and 12-month schedule of Prevnar 20 in infants and toddlers 6 weeks through 12 months of age in the U.S., Canada and Europe.

   Final Protocol Submission: March 23, 2020

   Study Completion Date: August 31, 2022

   Final Report Submission: December 31, 2022

4. Deferred pediatric study (B7471014) under PREA to evaluate the safety and immunogenicity of Prevnar 20 in children and adolescents 15 months through 17 years of age in the U.S.

   Final Protocol Submission: September 11, 2020

   Study Completion Date: December 31, 2022

   Final Report Submission: December 31, 2022

Submit the protocols to your IND 17980, with a cross-reference letter to this BLA 125731 explaining that these protocols were submitted to the IND.

Submit final study reports to this BLA 125731. For administrative purposes, all submissions related to these required pediatric postmarketing studies 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, Kamal Velmurugan, PhD, Juan Lacayo, PhD and Diana Oram, PhD.

Sincerely,

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