Our STN: BL 125508/868 **SUPPLEMENT ACCELERATED APPROVAL**

Merck Sharp & Dohme Corp. June 12, 2020
Attention: Anita Shaw, Ph.D.
351 N. Sumneytown Pike
P.O. Box 1000
UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

We have approved your request submitted and received December 13, 2019, to supplement your Biologics License Application (BLA) under section 351(a) of the Public Health Service Act for Human Papillomavirus 9-valent Vaccine, Recombinant (GARDASIL®9) to add prevention of oropharyngeal and other head and neck cancers caused by Human Papillomavirus (HPV) types targeted by the vaccine to the GARDASIL®9 indication, according to the regulations for accelerated approval, 21 CFR601.41.

The review of this supplement was associated with the following National Clinical Trial (NCT) numbers: NCT00365378, NCT00365716, NCT00092521, NCT00092534, NCT00090220, NCT00090285, NCT00543543, NCT00943722, NCT01651949, NCT00988884, NCT01047345, NCT01073293, and NCT01304498.

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 prevention of oral persistent infection with HPV Types 16, 18, 31, 33, 45, 52 or 58.

Accelerated Approval Required Studies

We remind you of your postmarketing requirement specified in your submission of June 6, 2020:

1. To conduct Study V503-049 to evaluate the efficacy of a three-dose regimen of GARDASIL®9 in the prevention of oral persistent infection with HPV types 16, 18, 31, 33, 45, 52 or 58 in men 20 through 45 years of age.

   Final Protocol Submission: October 29, 2019 (Completed)

   Study/Trial Completion: December 31, 2025

   Final Report Submission: September 30, 2026

We expect you to complete design, initiation, accrual, completion, and reporting of this study within the framework described in your letter of June 6, 2020.

You must conduct this study with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by Human Papillomavirus 9-valent Vaccine, Recombinant, 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

We acknowledge that your protocol was submitted to IND 13447. Please submit a cross reference letter to BLA 125508 explaining that this protocol was submitted to the IND. Please refer to the sequential number for each 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 BLA 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 BLA 125508. For administrative purposes, all submissions related to this postmarketing study requirement must be clearly designated as "Subpart E Postmarketing Study Requirements."

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 package insert and patient labeling submitted under amendment 125508/868.4, dated June 9, 2020.

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.

Please electronically submit all final content of labeling that is identical to the labeling submitted on June 9, 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-0.

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 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. 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 available at http://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)).

Please submit an amendment to all pending supplemental applications for this BLA that include revised labeling incorporating a revised content of labeling that includes these changes.

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 <9 years of age 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 note that you have fulfilled the pediatric study requirement for ages 9 to <17 years of age for this application.

We will include information contained in the above-referenced supplement in your BLA file.

Sincerely,

Doran L. Fink, M.D., Ph.D.
Deputy Director – Clinical
Division of Vaccines and
Related Products Applications
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research