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BLA Number 125752
Sequence No. 0003

August 24, 2021

Marion Gruber, PhD
Director, Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
Document Control Center
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Silver Spring, MD 20993-0002

Submission Type: Final Submission for Rolling Review Biologics License Application (BLA) - mRNA-1273 - Spikevax, REQUEST FOR PRIORITY REVIEW DESIGNATION, MATERIAL THREAT MEDICAL COUNTERMEASURE PRIORITY REVIEW VOUCHER REQUEST

Dear Dr. Gruber:

Reference is made to pre-assigned submission tracking number (STN) BLA 125752 for the initial Biologics License Application (BLA) for mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA)-based vaccine against the 2019 novel coronavirus (CoV; SARS-CoV-2).

Further reference is made to IND 019745, submitted to FDA on 27Apr 2021, and EUA 27073 authorized on 18Dec2020 for Emergency Use for mRNA-1273 (Moderna COVID-19 Vaccine) under Sections 564, 564A, and 564B of the Federal Food, Drug, and Cosmetic Act as amended or added by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013.

Final reference is made to BLA 127752 rolling review submissions SN0001 (Module 4) and SN0002 (Module 3).

The purpose of this submission is to submit the final rolling review submission for the Biologics License Application (BLA) for mRNA-1273, Spikevax, containing Modules 1, 2, and 5, and the request for priority review designation as well as the request for a material threat medical countermeasure (MCM) priority review voucher. The basis for the priority review request and the contents of the final rolling review submission are detailed below. Please refer to the note to reviewer for a complete list of documents included in this submission.

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The Moderna COVID-19 vaccine prevents a serious condition, which poses a material threat sufficient to affect national security and displays significant evidence of increased effectiveness and safety in the prevention of COVID-19. By way of this submission, the Sponsor is requesting the Agency for priority review as well as medical threat MCM priority review voucher.

Proper Name: mRNA-1273

Proprietary Name: Current under EUA: Moderna COVID-19 Vaccine; Proposed: Spikevax

Proposed Indication: Active immunization against coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus in persons 18 years of age and older.

Serious Condition:

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as MERS-CoV and SARS-CoV-1. An outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019, and the disease quickly spread globally. The Secretary of Health and Human Services (HHS) declared a public health emergency on 31 Jan 2020, under section 319 of the Public Health Service Act (42 U.S.C. 247d), in response to COVID-19 and the World Health Organization (WHO) declared COVID-19 a pandemic on 11 Mar 2020 . As of 26 Jul 2021, the WHO dashboard reports 4,162,304 COVID-19 deaths worldwide.

Evidence suggests that SARS-CoV-2 is transmitted via exposure to infectious respiratory fluids. Transmission of SARS-CoV-2 from asymptomatic or presymptomatic individuals has also been documented and may account for an estimated 59% of transmission. Common symptoms of COVID-19 include fever and cough, shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and loss of taste or smell. Individuals at highest risk of severe COVID-19 are older adults (≥ 65 years old) and people of any age who have certain underlying medical conditions, such as cancer, chronic kidney disease, chronic lung diseases, dementia or other neurological conditions, diabetes, Down syndrome, heart conditions, human immunodeficiency virus (HIV) infection, immunocompromised state, liver disease, obesity, pregnancy, sickle cell disease, solid organ transplant, and stroke or cerebrovascular disease.

The majority of individuals with COVID-19 have mild symptoms or moderate illness. Approximately 10% to 15% of COVID-19 cases progress to severe disease, and approximately 5% become critically ill. Long-term sequelae in COVID-19 patients with persistent symptoms after recovery from acute COVID-19 have been reported. Fatigue, dyspnea, joint pain, chest pain, and neuropsychiatric symptoms have been reported as common and persistent sequelae. Myocardial injury has been reported among patients with severe COVID-19. Additionally, some patients develop serious medical complications such as myocardial inflammation, ventricular dysfunction, pulmonary function abnormalities, and acute kidney injury. While more serious long-

term health complications appear to be less common, they have individual, global health, and severe socioeconomic consequences.

Moderna COVID-19 vaccine, mRNA-1273, Developed to Treat COVID-19:

The Sponsor has developed a rapid-response, proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The mRNA platform is based on knowledge of the established biology of cellular protein biosynthesis. mRNA is the 'blueprint' that cells use to synthesize the proteins needed for their physiology. Cells are able to uptake mRNA delivered in an LNP, translate the mRNA into its associated protein, and then express that protein viral antigen(s) on the cell surface to elicit an immune response. The delivered mRNA does not enter the cell nucleus or interact with the genome, is nonreplicating, and is only expressed transiently before undergoing degradation by the cell's natural mRNA degradation process. Several mRNA vaccines are in development and are being used to induce immune responses against infectious pathogens such as cytomegalovirus (CMV) (NCT03382405), human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) (NCT03392389), Zika (NCT04064905), and influenza virus (NCT03076385 and NCT03345043). The manufacturing process, which has been under development for 10 years, is cell-free and does not use vectors or animal products, preservatives or adjuvants.

Recognizing the broad potential of mRNA science, the mRNA technology platform was designed to function so that it could rapidly pivot to address this pandemic. The Sponsor was able to leverage the learnings of numerous vaccines in development, along with early pre-clinical work with other coronaviruses to select the appropriate antigen design to rapidly respond to the public need. mRNA-1273 encodes the full length SARS-CoV-2 spike protein stabilized in a prefusion conformation with 2 proline mutations.

Early in the pandemic, there was an internationally recognized and urgent public health need for the development of efficacious vaccines to prevent SARS-CoV-2. The Sponsor's scalable mRNA/LNP technology platform allowed for a rapid response to the pandemic and was used to develop mRNA-1273, a novel LNP-encapsulated mRNA-based vaccine against SARS-CoV-2.

The Moderna COVID-19 vaccine, mRNA-1273, has demonstrated anti-SARS-CoV-2 immune responses in Phase 1 (NCT04283461) and Phase 2 (NCT04405076) trials in adults, an acceptable safety profile, and 94% efficacy against symptomatic COVID-19 disease in the Phase 3 Coronavirus Efficacy (COVE) trial (NCT04470427) in more than 30,000 participants. Since December 2020, mRNA-1273 has been available under Emergency Use Authorization (EUA) and conditional approvals worldwide. As of 30 Jun 2021, 301,035,380 doses of mRNA-1273 have been distributed worldwide for use in adults 18 years of age and older.

Moderna COVID-19 vaccine, mRNA-1273, Demonstrated Significant Evidence of Effectiveness and Safety in the Prevention of COVID-19:

To date, nonclinical and clinical evaluations demonstrate that mRNA-1273 is well tolerated, immunogenic, and efficacious. Nonclinical immunogenicity, biodistribution, and safety studies were completed by the Sponsor using mRNA-1273 or similar mRNA-based vaccines formulated in SM-102–containing LNPs.

Based on the efficacy results from the Phase 3 study, mRNA-1273 prevents COVID-19 and, importantly, prevents severe COVID-19. The demonstrated clinical benefit of mRNA-1273 is supported by evidence of a robust immune response both in terms of bAbs and nAbs as well as the induction of CD4+ T-cells with a Th-1 dominant phenotype. Based on administration of mRNA-1273 to 15,704 adults across Study 301, Study 201, and Study 101, there have been no emergent safety concerns; the AE profile is predominantly characterized by mild to moderate reactogenicity lasting 2 to 3 days.

Statistically significant VE to prevent COVID-19 was demonstrated in adults ≥ 18 years of age during the ongoing pandemic. Vaccine efficacy was 94.1%, 94.5%, and 93.2% at the interim, primary, and final efficacy analyses, respectively, confirming persistent, high efficacy over a median blinded observation period of 5.3 months. These VE point estimates exceeded regulatory guidance which suggested 50% efficacy with a lower bound CI of at least 30% for vaccines in development during the pandemic. Importantly, mRNA-1273 was 98.2% effective in preventing severe COVID-19; this is a clinically relevant result because severe COVID-19 is associated with increased hospitalizations and mortality. mRNA-1273 also demonstrated protection against asymptomatic SARS-CoV-2 infection. The VE to prevent asymptomatic SARS-CoV-2 infection was 63.0%, and VE to prevent SARS-CoV-2 infection, regardless of symptomatology or severity, was 82.0%.

Vaccination with mRNA-1273 generally resulted in transient local injection site and systemic reactions and were noted to occur at a lower frequency in older adults compared with younger adults. The majority of the ARs were considered risks with minimal and temporary clinical impact. The incidence of SAEs was low, and rates were similar in the mRNA-1273 and placebo groups. Unsolicited TEAEs in the 28 days after any injection occurred at similar rates in the mRNA-1273 and placebo groups. The higher rate of unsolicited TEAEs considered treatment-related by the investigator among mRNA-1273 participants was largely driven by events that mapped to solicited ARs. mRNA-1273 was highly efficacious in preventing COVID-19 and severe COVID-19, and this efficacy has been sustained, dispelling concerns of VAERD. No significant clinical findings were identified from the SMQ/CMQ searches performed for the analyses of AEs of interest for COVID-19 vaccines.

Outside the clinical studies, the number of persons vaccinated with COVID-19 vaccines within the period since authorization has been unprecedented in vaccine history. The rollout of COVID-19 vaccines has also been associated with extensive post-authorization safety monitoring noted as the most intensive safety monitoring in US vaccine history.

Based on the data presented in this submission, mRNA-1273 is a highly effective vaccine with an acceptable safety profile for the prevention of COVID-19 in adults 18 years of age and older. Considering the ongoing public health emergency due to SARS-CoV-2, the available safety and efficacy data from the 3 clinical studies presented herein, and the ongoing post-authorization surveillance, the Sponsor believes mRNA-1273 prevents a serious condition where there are no other preventative modalities approved, demonstrates significant evidence of increased effectiveness and safety in the prevention of COVID-19, and therefore is eligible for priority review.

Material Threat Medical Countermeasure (MCM):

Based upon the data provided in the priority review request, the Sponsor believes the Moderna COVID-19 vaccine, mRNA-1273, qualifies as a medical countermeasure that is intended to prevent a serious condition that results in adverse health consequences or death. Therefore, this Biologics Licenses Application, which is defined as a human drug application under section 735(1) of the FD&C Act (21 U.S.C. 379g(l)), qualifies as a material threat medical countermeasure application under section 565A(a)(4) of the FD&C Act and is eligible for a medical threat medical countermeasure (MCM) priority review voucher request.

If FDA has any questions, please do not hesitate to contact me directly at (617) 417-4428 or at michelle.olsen@modernatx.com.

This eCTD submission has been prepared by PPD Development, Inc. in full compliance with ICH and FDA guidance. The eCTD has been verified and confirmed to be virus and spyware free. PPD utilizes Palo Alto Traps v4.2.2. All technical questions should be directed to Mr.Eric Malamutt at PPD (910) 558-8871 or email at eric.malamutt@ppd.com.

Yours Sincerely,

Michelle Olsen

Digitally signed by Michelle Olsen
Date: 2021.08.23 11:26:15 -04'00'

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NOTE TO REVIEWER

Included in this submission are the remaining Modules to complete the rolling review submissions for BLA #125752 (Module 1, Module 2, and Module 5). The content in each Module are included in the table at the end of this document.

The Sponsor engaged the Agency in two pre-BLA requests for information with regards to the content of this submission:

- Clinical, non-clinical, and pharmacovigilance (PV)
    - Briefing Document submitted: IND 19745 SN0127 31Mar2021
    - Responses received: 28Apr2021
- Regulatory:
    - Briefing Document submitted: IND 19745 SN0154 25May2021
    - Responses received: 01July2021

With regards to the first pre-BLA engagement regarding Clinical and PV, in addition to what was proposed in the briefing document, the Agency requested a number of additional items/information. The requests and how they were incorporated into this BLA submission are outlined as follows:

- Longer term follow-up for P201: P201 Day 209 CSR addendum is included
- CRFs for severe COVID-19 cases: included in CSR appendices
- Narratives for severe COVID-19 cases: included in CSR
- Cumulative analysis of post-authorization safety data: included in Module 2.7.4 (Section 2.7.4.6), and Monthly Safety Report #6 with a data cutoff of 30June2021 is included in Module 5.3.6 as supportive.
- Clinical Assays for Study Endpoints: all assay documentation is included in subfolders within Module 5.3.1.4; additionally, a background document with an overview fo the assay information is included in Module 5.3.1.4.

In addition, the Agency agreed with the proposed data package for the pivotal study (P301), and agreed that no integrated summaries or datasets were needed.

With regards to the pre-BLA engagement regarding Regulatory questions, the Agency agreed to the Sponsor submitting both a priority review designation, and a request for material threat medical countermeasure priority review voucher. These requests are included in the cover letter for this submission. The Agency also agree to accept the EU RMP for the pharmacovigilance plan. With regards to an environmental analysis (EA), the Agency asked for additional information to determine whether mRNA-1273 qualifies for categorical exclusion. A more detailed EA has been included in Module 1.

Submission Content:

Module 1	
1.1.2	356h /BLA
1.1.7	3674 Certification of Compliance with Requirements of ClinicalTrials.gov
1.2	**Cover letters**
	Cover Letter/ Note to reviewer
1.3	**Administrative information**
1.3.1	Contact/sponsor/applicant information
1.3.1.4	Transfer of obligation
1.3.3	Debarment certification
1.3.4	Financial certification and disclosure
	3454 P301 + list of investigators
	3454 P201 + list of investigators
1.4	**References**
1.4.4	Cross-reference to previously submitted information
1.6	**Meetings**
1.6.1	Meeting request
1.9	**Pediatric administrative information**
1.9.2	Request for deferral of pediatric studies
1.9.6	Other correspondence regarding pediatric exclusivity or study plans
	Agreed iPSP
	Letter of Agreement FDA
1.12	**Other correspondence**
1.12.14	Environmental analysis
1.14	**Labeling**
1.14.1	**Draft labeling**
1.14.1.1	Draft carton and container labels
	Draft Vial Label 5.5mL
	Draft Vial Label 7.5mL
	Draft Carton 5.5mL
	Draft Carton 7.5mL
1.14.1.2	**Annotated draft labeling text**
	Draft Labeling Text-Annotated
1.14.1.3	**Draft labeling text**
	Draft Labeling Text-Prescribing Information-Clean (Word)
	Draft Labeling Text-Prescribing Information-Clean (PDF)
	Draft Labeling Text-Patient Information-Clean (Word)
	Draft Labeling Text-Patient Information-Clean (PDF)
	Draft Labeling Text-SPL
1.16	**Risk management plan**

1.18	**Proprietary names**
	Request for Proprietary Name Review
Module 2	
2.2	**Introduction to summary**
2.3	**Quality overall summary**
	2.3 QOS Introduction
	2.3 QOS Drug Substance - CX-024414
	2.3 QOS Drug Substance - mRNA-1273 LNP
	2.3 QOS Drug Product
	2.3 QOS Appendices
2.4	Non-Clinical Overview
2.5	**Clinical overview**
2.6	**Nonclinical written and tabulated summaries**
2.6.1	Introduction
2.6.2	Pharmacology written summary
2.6.3	Pharmacology tabulated summary
2.6.4	Pharmacokinetic written summary
2.6.5	Pharmacokinetic tabulated summary
2.6.6	Toxicology written summary
2.6.7	Toxicology tabulated summary
2.7	**Clinical summary**
2.7.2	Summary of Clinical Pharmacology studies
2.7.3	Summary of Clinical Efficacy [**indication**]
2.7.4	Summary of Clinical Safety
2.7.5	References
2.7.6	Synopses of individual studies
Module 5	
5.2	**Tabular listing of all clinical studies**
	Tabular Listing of All Clinical Studies
5.3	**Clinical study reports and related information**
5.3.1	**Reports of biopharmaceutic studies**
5.3.1.4	Reports of bioanalytical and analytical methods for human studies
	ELISA: S2Pprotein IgG
	VSDVAC 58 ELISA IgG Sprotein Qualification Statistical Report
	VSDVAC 65 ELISA IgG Sprotein Method Validation Report v1.01
	VSDVAC 65 ELISA IgG Sprotein Method Validation Report Adden 1
	VSDVAC 65 ELISA IgG Sprotein Method Validation Report Adden 2
	VSDVAC 65 ELISA IgG Sprotein Method Validation Report Adden 3
	VSDVAC 65 ELISA IgG Sprotein Method Validation Report Adden 4
	VSDVAC 65 ELISA IgG Sprotein Method Validation Report Adden 5
	VSDVAC 65 Method (version 1.02)

	ELISA: Nprotein IgG
	VSDVAC 64 ELISA IgG Nprotein Qualification Statistical Report
	VSDVAC 66 ELISA IgG Nprotein Method Validation Stat Report
	VSDVAC 66 ELISA IgG Nprotein Method Validation Report Adden 1
	VSDVAC 66 ELISA IgG Nprotein Method Validation Report Adden 1 Amdt 1
	VSDVAC 66 ELISA IgG Nprotein Method Validation Report Adden 1, Antigen 01
	VSDVAC 66 ELISA IgG Nprotein Method Validation Report Adden 2
	VSDVAC 66 ELISA IgG Nprotein Method Validation Report Adden 3
	VSDVAC 66 ELISA IgG Nprotein Method Validation Report Adden 3, Amdt 1
	VSDVAC 66 SOP
	ELECSYS: Nprotein IgG
	ELECSYS AntiSARSCoV2 Package Insert. Roche Diagnostics.
	VRGCLUS2020065512 Elecsys IgG Nprotein Method Validation Report Version 02
	SOP-18550
	MSD Singleplex: Sprotein IgG
	B1004 V MSD IgG Sprotein Validation Report
	R1023 MSD IgG Sprotein Validation Report Adden 1
	R1022 MSD IgG Sprotein of Incurred Samples for OWS Validation Report
	R1024 MSD IgG Sprotein of Incurred Samples for OWS Validation Report Adden 1
	SOP5525
	Live Virus MN
	QA5858 Qualification of the SARSCoV2 Microneutralization Assay
	VA5933STATSCSR Validation Report
	VA6003 Partial Validation Phase 1 mRNA1273 Samples
	SOP BBR.C.X-339-01
	PsVNA
	COVID0001 Method Validation Statistical Report v1.0
	COVID0001 Method Validation Statistical Report Adden. 1 v1.1
	COVID0002 Method Validation Statistical Report
	CFAR02 A0026
	Biomarker Concordance
	Moderna 1273 Biomarker Concordance Analysis Report for Study 301
	RTqPCR
	21120.8918 SARSCoV2 (COVID19) RTqPCR Validation Report Version 3.0
	21120.9249 SARSCoV2 RTqPCR Swab and IsohelixSaliva Validation Report Version 1.0
	SOP: 21120.9204
	RTPCR BioFire FilmArray® RP
	21120.8062 Qualification Report of the BioFire FilmArray® Respiratory Panel
	SOP 21120.2380
	RTPCR NGS
	21120.10208 NGS Validation Report Version 1.0
	SOP: 21120.10120

	RTPCR WGS
	21120.10562 SARSCoV2 WGS Verification Report Version 1.0
	SOP: 21120.10517
5.3.5	**Reports of efficacy and safety studies**
5.3.5.1	**Study reports and related information of controlled clinical studies pertinent to the claimed indication**
	CSR P301
	Synopsis
	Report Body
	eSub package
	BIMO
	16.1 Study Information
	16.1.1 Protocol and protocol amendments
	16.1.2 Sample case report form
	16.1.3 List of IECs or IRBs
	16.1.4 List and description of investigators and other important participants in the study
	16.1.5 Signatures of principal or coordinating investigator(s)
	16.1.6 Listing of patients receiving test drug(s)/investigational product(s)
	16.1.7 Randomization scheme and codes
	16.1.8 Audit certificates (if available)
	16.1.9 Documentation of statistical methods
	16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used
	16.1.11 Publications based on the study
	16.1.12 Important publications referenced in the report
	16.1.13
	16.2 Patient Data Listings
	16.2.1 Discontinued patients
	16.2.2 Protocol deviations
	16.2.3 Patients excluded from the efficacy analysis
	16.2.4 Demographic data
	16.2.5 Compliance and/or drug concentration data (if available)
	16.2.6 Individual efficacy response data
	16.2.7 Adverse event listings (each patient)
	16.2.8 Listing of individual laboratory measurements by patient
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	16.4 Individual Patient Data Listings
	CSR P301 Addendum
	Synopsis

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	16.1.1 Protocol and protocol amendments
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	16.2.8 Listing of individual laboratory measurements by patient
	16.3 Case Report Forms (CRFs)
	16.4 Individual Patient Data Listings
	CSR P201 Addendum
	Synopsis
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	16.1 Study Information
	16.1.1 Protocol and protocol amendments
	16.1.2 Sample case report form
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	16.1.5 Signatures of principal or coordinating investigator(s)
	16.1.6 Listing of patients receiving test drug(s)/investigational product(s)

	16.1.7 Randomization scheme and codes
	16.1.8 Audit certificates (if available)
	16.1.9 Documentation of statistical methods
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	16.2.8 Listing of individual laboratory measurements by patient
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	16.3 Case Report Forms (CRFs)
	16.4 Individual Patient Data Listings
5.3.5.2	**Study reports and related information of uncontrolled clinical studies**
	CSR P1 D119 CSR
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	CSR P1 Addendum
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	16.4 Individual Patient Data Listings
5.3.6	**Post-Authorization Monthly Safety Report #6**
5.4	**Literature references**