U.S. FOOD & DRUG ADMINISTRATION

Information Request

Our Reference: STN: 125752/2

Information Request #31

Date: December 10, 2021

To: **Michelle Olsen, Ph.D.**
ModernaTX, Inc.
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From: **Joseph Kulinski, Ph.D.**
DVRPA/OVRR/CBER
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Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Postmarketing Requirement/Commitment (PMR/PMC) studies

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We have the following request for additional information Postmarketing Requirement/Commitment (PMR/PMC) studies:

A. Should this product be approved, we have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) will not be sufficient to identify:
   - known serious risks of myocarditis and pericarditis
   - an unexpected serious risk of subclinical myocarditis

   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, should this product be approved, we have determined that you will be required to conduct the following studies as postmarketing requirements (PMRs) under Section 505(o) of FDCA:

   1. Study mRNA-1273-P903, entitled “Post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity”, to

evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.

2. Study mRNA-1273-P904, entitled “Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe,” to evaluate the occurrence of myocarditis and pericarditis following administration of SPIKEVAX.

3. Study mRNA-1273-P911, entitled “Long-term outcomes of myocarditis following administration of SPIKEVAX (Moderna COVID-19, mRNA-1273),” to evaluate long-term sequelae of myocarditis after vaccination with at least 5 years of follow-up.

4. Study mRNA-1272-P301 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 18 years of age and older.

5. Study mRNA-1273-P203 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a booster dose of SPIKEVAX in participants 12 to <18 years of age.

6. Study mRNA-1273-P204 substudy to prospectively assess the incidence of subclinical myocarditis following administration of SPIKEVAX in a subset of participants 6 months to <12 years of age.

Additionally, should this product be approved, your proposed studies listed below will be postmarketing commitments (PMCs) as agreed upon between FDA and the applicant:

1. Study mRNA-1273-P901, entitled “Real-World Study of the Effectiveness of Moderna COVID-19 Vaccine.”

2. Study mRNA-1273-P902, entitled “Moderna mRNA-1273 Observational Pregnancy Outcome Study.”

3. Study mRNA-1273-P905, entitled “Monitoring safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries.”

B. Please populate the table below with your study milestone dates (mm/dd/yyyy) for final protocol submission, study completion and final study report submission for each PMR/PMC study. Note that comments on Study mRNA-1273-P903

protocol have been previously communicated to Moderna, and the final study protocol submission should address FDA recommendations and comments.

	Final protocol submission date	Study completion date	Final study report submission date
Study mRNA-1273-P903			
Study mRNA-1273-P904			
Study mRNA-1273-P911			
Study mRNA-1273-P901			
Study mRNA-1273-P902			
Study mRNA-1273-P905			
Study mRNA-1273-P301 substudy			
Study mRNA-1273-P203 substudy			
Study mRNA-1273-P204 substudy			

C. Please refer to study mRNA-1273-P911: We have the following requests:

1. Enroll at least 300 subjects with myocarditis after vaccination with SPIKEVAX

2. Modify inclusion criteria from “Onset within 30 days of Moderna COVID-19 vaccination” to “Onset within **7 days** of Moderna COVID-19 vaccination”

Please acknowledge that the final study protocol mRNA-1273-P911 will address the above FDA requests.

D. Please include the PMRs and PMCs (listed in section A of this information request) in your updated Pharmacovigilance Plan (PVP) and submit an updated PVP (tracked change and clean versions) to the BLA.

Please confirm your receipt of this request and submit your response as an amendment to STN 125752 as soon as possible but no later than December 13, 2021.

Please contact me if you have questions and include Sudhakar Agnihothram (sudhakar.agnihothram@fda.hhs.gov) and Joseph Kulinski (josephine.resnick@fda.hhs.gov) on all communications.