DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review
(b) (6)

Chair Review Memorandum

Date: September 26, 2025

STN: 125835/6

From: (b) (6)

Through: (b) (6)

(b) (6)

Applicant: ModernaTX, Inc.

Product: COVID-19 Vaccine, mRNA (MNEXSPIKE)

Supplement Type: Efficacy Supplement

Submission Date: June 6, 2025

Action Due Date: April 6, 2026

---

1. Background:

The following pre-submission regulatory events and activities are pertinent to the review of this submission:

- The Applicant submitted an original Biologics License Application (STN 125835/0) for their COVID-19 Vaccine, mRNA (MNEXSPIKE) on September 30, 2024, which received approval on May 30, 2025, for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals who have been previously vaccinated with any COVID-19 vaccine and are 65 years of age and older, or 12 years through

64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. The original approval of MNEXSPIKE was formulated with the 2024-2025 Formula (JN.1 strain).

- Following the original BLA approval for MNEXSPIKE, a labeling supplement (STN 125835/12) was submitted on June 23, 2025, and approved on July 3, 2025, to include the estimated unadjusted incidence of myocarditis and/or pericarditis during the period 1 through 7 days following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines in males 12 years through 24 years of age in the Warnings and Precautions section of the Package Insert and in the Patient Package Insert.

- FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) met on May 22, 2025, to discuss and make recommendations on the selection of the 2025-2026 Formula for COVID-19 Vaccines (2025-2026 Formula) for Use in the United States Beginning in Fall 2025 | FDA. Following the VRBPAC meeting, FDA issued an advice letter to the Applicant on May 22, 2025, recommending that they develop a monovalent JN.1-lineage based COVID-19 vaccine for use in potentially eligible populations, with the preferred JN.1-lineage for the COVID-19 vaccines (2025-2026 Formula) being the LP.8.1 strain.

- The CBER Office of the Center Director (OCD) issued an FDA advice letter to the Applicant on June 4, 2025, requesting submission of an efficacy supplement to their original BLA STN 125835 for the MNEXSPIKE 2025-2026 Formula using the LP.8.1 strain by June 6, 2025. The request was for the supplement to include Chemistry, Manufacturing and Control (CMC) information, nonclinical data, clinical safety and immunogenicity data from previously unvaccinated participants in Study mRNA-1283-P301 and subgroup analyses of relative vaccine efficacy for participants at higher risk for severe COVID-19. Additionally, the Applicant was asked to provide protocol concept sheets for 506B postmarketing commitment (PMC) studies to evaluate safety and immunogenicity in the approved populations, with a second study for previously unvaccinated participants required only if existing data were unavailable (see 6. Postmarketing Agreements for additional details).

2. Submission Summary:

In response to CBER OCD's June 4, 2025, regulatory advice letter, the Applicant submitted an efficacy supplement to update the monovalent JN.1-based MNEXSPIKE (2024-2025 Formula) to a monovalent Omicron sublineage LP.8.1-based MNEXSPIKE (2025-2026 Formula) for use in the United States beginning Fall of 2025. The submission included associated labeling changes (i.e., USPI, PPI, carton and container labels), a postmarketing commitment study protocol concept sheet to evaluate safety and immunogenicity of MNEXSPIKE (2025-2026 Formula) in participants 65 years of age and older and in participants 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19, and data from Study mRNA-1283-P301 Part 1 subgroup analyses of relative vaccine efficacy for participants meeting CDC-defined criteria for 'higher risk for severe COVID-19'. Additionally, the Applicant provided safety and immunogenicity data from Study mRNA-1283-P301 Part 2 for previously unvaccinated participants in the target populations and

based on these data, requested to expand the use of MNEXSPIKE from being restricted to COVID-19 vaccine-experienced individuals to also include COVID-19 vaccine-naïve individuals.

3. Summary of Regulatory Activity:

Information Requests

The Applicant received and responded to 16 information requests (IRs) associated with this supplement, and the review team determined that all responses were acceptable. Details regarding IRs, along with corresponding amendments and review verification can be found in the Documentation Review Memo.

Environmental Assessment

The Applicant included a request for categorical exclusion from the requirement to provide an environmental assessment. The CMC reviewer determined this request was acceptable.

Unique Ingredient Identifier (UNII) Codes

A UNII Code Assignment Letter was issued to the Applicant on August 26, 2025. The letter assigned UNII Code KFZ2Z65LB6 to the active ingredient (CX-052075) in the Applicant's MNEXSPIKE 2025-2026 Formula vaccine. Note that the excipients for this product remain unchanged from the May 30, 2025, approval.

Lot Release/Clearance

The (b) (6) completed a lot release check on July 29, 2025, and identified 19 lot numbers associated with this supplement. (b) (6) indicated that these lots would be released upon completion of protocol review, any requested sample testing and approval of the supplement.

Compliance Check

The (b) (6) completed a compliance check on August 12, 2025, and indicated there were no ongoing or pending investigations or compliance actions with respect to the manufacturing facilities associated with this supplement.

4. Review Summaries

Chemistry Manufacturing and Controls (CMC) and Nonclinical

The CMC information submitted in STN 125835/6.0, and subsequent amendments supports the approval of the monovalent 0.05 mg/mL mRNA-1283.251 (Omicron variant sublineage LP.8.1) vaccine formulation in a single-dose pre-filled syringe (PFS) with a 0.2 mL nominal fill volume presentation manufactured and tested at (b) (4) (b) (4) and Moderna Biotech Spain S.L.

A detailed review of the supportive CMC and nonclinical information can be found in the CMC Review Memo.

Clinical/Biostatics

Descriptive relative vaccine efficacy (rVE) data from Study mRNA-1283-P301 Part 1 provides supportive evidence for MNEXSPIKE vaccine effectiveness in the population of individuals 12 through 64 years of age with at least one high risk condition for severe COVID-19. Data from Study mRNA-1283-P301 Part 3 supports the safety and effectiveness of MNEXSPIKE in individuals who are COVID-19 vaccine-naïve. No safety concerns were identified from either study.

A detailed review of the study data can be found in the Clinical and Biostatistical Review Memos.

Bioresearch Monitoring (BiMo)

Under the original BLA (STN 125835/0), six BiMo inspections (five clinical investigator and one sponsor) were conducted between March and April 2025 for the pivotal study mRNA-1283-P301, and all were classified as “No Action Indicated”. No additional BiMo inspections were warranted for this supplemental application.

Pharmacovigilance

No updates were made to the MNEXSPIKE pharmacovigilance plan (PVP), as confirmed by the Applicant in their June 17, 2025, response to the pharmacovigilance consult reviewer’s June 13, 2025, IR.

Following the July 3, 2025, approval of labeling supplement STN 125835/12, the Applicant incorporated the approved safety labeling into the MNEXSPIKE (2025-2026 Formula) USPI under review for STN 125835/6.

Given that no PVP updates were made, the approved safety labeling was incorporated from STN 125835/12 into the USPI for STN 125835/6, and there were no postmarketing data to review, no additional pharmacovigilance review was needed for STN 125835/6.

Labeling

The Applicant submitted product labeling for MNEXSPIKE (2025-2026 Formula) for CBER review, including USPI, PPI, and carton/container labels. Refer to the regulatory and (b) (6) Labeling Review Memos for details on the labeling review process for MNEXSPIKE (2025-2026 Formula), including meetings, negotiations, materials reviewed, and final approved content.

Data Validation and Data Integrity

Validation of analysis and tabulation datasets for Study mRNA-1283-P301 Part 3 (COVID-19 vaccine-naïve cohort) was conducted by the CBER (b) (6) on

July 16, 2025, to support the expansion of use of MNEXSPIKE in COVID-19 vaccine-naïve individuals. The review team's assessment of the validation results revealed no significant issues that would impact review of the datasets.

Separately, a comprehensive review of the submitted datasets prompted several IRs from the review team to the Applicant, as detailed in the Documentation Review Memo. The Applicant's responses were found acceptable.

In summary, the Data Integrity reviewer determined that the datasets were adequate for review, but identified several considerations that were communicated to the Applicant for future submissions. Additional details and a complete review can be found in the Data Integrity Review Memo.

5. Regulatory Considerations:

On August 21, 2025, CBER OCD notified the Applicant that a signal of risk exists for Post-COVID-19 Vaccination Syndrome (PCVS), potentially linked to persistence of vaccine-derived spike protein in recipients. CBER OCD requested that the Applicant conduct a comprehensive 506B PMC study to assess additional monitoring for spike protein persistence. The Applicant submitted their proposal on August 27, 2025, in amendment 25 (see 6. Postmarketing Agreements). The proposed study design, objectives, and milestone dates were reviewed by CBER OCD and determined to be acceptable.

6. Postmarketing Agreements

CBER OCD requested the Applicant include protocol concept sheets for the following PMC studies in their submission:

> Study 1: Prospectively designed study to evaluate safety and immunogenicity of MNEXSPIKE (2025-2026 Formula) in participants 65 years of age and older and in participants 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. The study should be adequately powered for prespecified hypothesis testing of study immunogenicity endpoints for each age group in which MNEXSPIKE is approved for use.
>
> Study 2: Prospectively designed study to evaluate safety and immunogenicity of MNEXSPIKE (2025-2026 Formula) in previously *unvaccinated* participants 65 years of age and older and 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19.

In the initial submission, the Applicant submitted a protocol concept sheet for Study 1. Following review of the concept sheet by CBER OCD, an IR was issued on July 24, 2025, requesting that the Applicant submit a revised study design for Study 1 to IND 27196 based on specific success criteria outlined in the IR. The Applicant's proposed milestone dates for this PMC were based on the current status of their mRNA-1283-P401 study, and were determined to be acceptable by the CBER OCD.

Below are the agreed upon Section 506B PMCs and their corresponding milestones for STN 125835/6 that were included in the August 27, 2025, approval letter:

1. A Phase 3b/4, Open-label, Single Arm Study to Evaluate the Immunogenicity and Safety of mRNA-1283.251 in Individuals ≥65 Years and ≥12 to <65 Years with Risk Factors for Severe COVID-19 (mRNA-1283-P401 Subprotocol 01).

   Final Protocol Submission: June 20, 2025
   Study Initiation: July 21, 2025
   Protocol Amendment Submission: September 30, 2025
   Part A Data Memo: December 31, 2025
   Part B Interim Results: April 30, 2026
   Study Completion: May 31, 2026
   Final Report Submission: October 31, 2026

2. A Phase 4 Randomized, Observer Blind, Placebo-controlled Study to Evaluate the Safety of mRNA-1273 and mRNA-1283 Variant-containing Formulations in Adults 50 to 64 Years of Age without High-Risk Conditions for Severe COVID-19.

   Study Initiation: November 30, 2025
   Study Completion: January 31, 2027
   Final Report Submission: January 31, 2028

   For this study, the Applicant proposes an additional exploratory objective to evaluate circulating levels of Spike protein as well as assessing symptoms using a Long COVID questionnaire administered at Month 1, Month 3, Month 6, and Month 12 Post-vaccination.

For Scientific and Regulatory Rationale (as per CBER SOPP 8415) for requesting the agreed upon postmarketing commitments, please refer to the Center Director Decisional Memos dated May 30, 2025 (STN 125835/0), and August 26, 2025 (STN 125835/6).

7. Recommended Regulatory Action:

Based on a comprehensive review of the clinical data, CMC information, and labeling included in this efficacy supplement, the Review Committee recommends approval of STN 125835/6 to include the 2025-2026 Formula and associated labeling revisions.

The Final Draft Package Insert and Patient Package Insert were provided as part of the approval package for web posting.