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:	125752/305
From:	(b) (6)
Through:	(b) (6)
	(b) (6)
Applicant:	ModernaTX, Inc.
Product:	COVID-19 Vaccine, mRNA (SPIKEVAX)
Supplement Type:	Prior Approval Supplement (Efficacy)
Submission Date:	May 23, 2025
Action Due Date:	March 23, 2026

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1. Background

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) was convened on May 22, 2025, to discuss and make recommendations on the selection of the 2025-2026 Formula for COVID-19 vaccines for use in the United States beginning in the Fall of 2025. Following the VRBPAC meeting, FDA issued a regulatory 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, and that the preferred JN.1-lineage for the COVID-19 vaccines (2025-2026 Formula) is the LP.8.1 strain.

In response to the May 22, 2025, FDA advice letter on the COVID-19 vaccine 2025-2026 Formula, the Applicant submitted a Prior Approval Supplement (PAS) to STN 125752 on

May 23, 2025. The purpose of this submission is to update SPIKEVAX from the current KP.2 -based 2024-2025 Formula to an LP.8.1-based 2025-2026 Formula.

2. Submission Summary

The May 23, 2025, initial submission under STN 125752/305 included supporting chemistry, manufacturing, and controls (CMC) data, nonclinical information, and corresponding labeling updates, including revisions to the U.S. Prescribing Information (USPI), Patient Package Insert (PPI), and carton and container labeling. On May 27, 2025, the CBER Office of the Center Director (OCD) issued an addendum to the May 22, 2025, FDA advice letter to the Applicant, requesting that the Applicant submit an amendment to their Supplement (STN 125752/305) to include human safety and immunogenicity data for SPIKEVAX (2025-2026 Formula), along with an updated cover letter and 356h form requesting a revised indication and corresponding labeling for SPIKEVAX for use in individuals 65 years of age and older or 6 months through 64 years of age with at least one underlying condition. Additionally, the Applicant was requested to provide protocol concept sheets for postmarketing commitment (PMC) studies to assess the following:

1) Safety and immunogenicity of SPIKEVAX in participants 65 years of age and older and 6 months through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID-19

2) Safety and efficacy of SPIKEVAX in individuals 50 through 64 years of age without an underlying condition that puts them at high risk for severe outcomes from COVID-19.

The Applicant submitted Amendment 1 to STN 125752/305 on June 4, 2025, to include the additional information requested in the May 27, 2025, CBER OCD advice letter addendum. Under STN 125752/305.1, the Applicant included a cover letter requesting that the CMC PAS submitted on May 23, 2025, as BLA 125752/305 be converted into an efficacy supplement along with a request to update the indication for the SPIKEVAX (2025-2026 Formula) as reflected on the updated Form FDA 356h.

Table 1: Summary of STN 125752/305.0 and Amendment 1 contents

	Contents	**Submission**
Module 1	Carton/Container labeling, PI, PPI, Risk Management plan (v10.2)	125752/305.0
	Updated 356h for Efficacy PAS, Updated Cover Letter with requests Re-categorization as an Efficacy Supplement and update to indication as well as Revised USPI and PPI to align with updated indication	125752/305.1
Module 2	Quality summary, Nonclinical introduction/summaries	125752/305.0
Module 3	Manufacturing, facility and testing info to support updates for CX-051869 DS, mRNA-1273.251 (b) (4) Drug Substance, and mRNA-1273.251 Drug Product	125752/305.0
Module 4	Nonclinical Study Reports Mod-7407 and Mod-7345	125752/305.0
Module 5	Literature references	125752/305.0
	CSR and Datasets for Clinical Study P403 Subprotocol 2, PMC study protocol concepts sheets for PMC 1 and PMC 2	125752/305.1

3. Summary of Regulatory Activity

Information Requests
There were 14 information requests associated with this supplement that were issued to the Applicant. The Applicant responded to all these requests in a timely manner and those responses were routed to the requestor(s) for review. Details regarding information requests, 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 20, 2025. The letter assigned UNII Code KFZ2Z65LB6 to the active ingredient (CX-052075) in the Applicant's SPIKEVAX 2025-2026 Formula vaccine.

Lot Release/Clearance
The (b) (6) completed a lot release check on July 30, 2025, and identified 16 lots associated with this supplement. (b) (6) indicated that these lots will be released upon completion of protocol review, any requested sample testing and approval of the supplement.

Compliance Check
(b) (6) completed a compliance check on August 25, 2025, and indicated there are 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 and nonclinical information submitted in STN 125752/305 and subsequent amendments supports the implementation of the SPIKVEVAX mRNA-1273.251 (Omicron variant sublineage LP.8.1) vaccine formulation in a single-dose pre-filled syringe (PFS) presentation with a 0.25 mL or 0.5 mL nominal fill volume. A detailed review of the supportive product and nonclinical information can be found in the CMC review memo. Additional details regarding analytical methods used for lot release of SPIKEVAX (2025-2026 Formula) Drug Substance (DS) and Drug Product (DP) can be found in the (b) (6) Analytical Method Review Memo.

Clinical
In Amendment 1 to STN 125752/305, the Applicant submitted a final clinical study report and associated datasets from Study mRNA-1273-P403 Subprotocol 02, a Phase 3b/4 single-arm, open-label study to assess the safety and immunogenicity of a single dose of mRNA-1273.712 [SPIKEVAX (2024-2025 Formula)] in 50 healthy adults 18 years of age and older who were previously vaccinated against COVID-19. No safety signals were identified from this study, which had a follow-up duration of 1-month postvaccination. Given that LP.8.1 is also a SARS-CoV-2 variant within the JN.1-lineage, the submitted clinical trial data from adults vaccinated with the KP.2-based SPIKEVAX (2024-2025 Formula), combined with nonclinical data evaluating the LP.8.1-based SPIKEVAX (2025-2026 Formula), support the proposed formula update. A detailed review of the clinical information can be found in the clinical review memo.

Stats
There were no major statistical issues identified. A detailed review of the statistical information can be found in the statistical review memo.

Pharmacovigilance
From the safety data submitted, the review team determined that there were no new safety signals among participants who received SPIKEVAX. Review of the Applicant's post-authorization and postmarketing safety data, VAERS data, and data mining findings for SPIKEVAX did not reveal any new safety concerns. The Applicant has several outstanding safety-related postmarketing requirement (PMR) and postmarketing commitment (PMC) studies (as specified in the original BLA approval letter), for which interim and final reports will be submitted to the BLA. Additionally, the safety profile of SPIKEVAX (2024-2025 Formula) has been evaluated in several of these studies, including Study P951, which was designed to enroll participants across all age cohorts. A detailed Pharmacovigilance review of this submission can be found in the (b) (6) Pharmacovigilance review memo.

Labeling
The Applicant submitted product labeling for SPIKEVAX (2025-2026 Formula) for CBER review, including the U.S. Prescribing Information (USPI), Patient Package Insert (PPI), and carton and container labels. A detailed summary of labeling review can be found in the labeling review memo and (b) (6) memo.

Clinical Data Validation
SDTM and ADaM standardized datasets from study mRNA-1273-P403 (P403) underwent validation by the CBER (b) (6) The review team's assessment of the validation results revealed no significant issues that would impact review of the datasets.

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 that combines an existing Phase 4 randomized controlled trial with additional monitoring for spike protein persistence. The Applicant submitted their proposal on August 16, 2025, in amendment 26, (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

In Amendment 1 to STN 125752/305, the Applicant submitted PMC study Concept Sheets for the following studies as requested in the May 27, 2025, CBER OCD-requested Regulatory Advice Addendum:

- Study 1: A Phase 4, Open-label, Single Arm Study to Evaluate Immunogenicity and Safety of mRNA-1273 Variant-containing Formulation in Individuals ≥65 years and ≥12 to <65 years with Risk Factors for Severe COVID-19.
- Study 2: A Phase 4, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of mRNA-1273 variant-containing formulation in adults 50 to 64 years of age Without Risk Factors for Severe COVID-19.

Subsequently, CBER OCD issued an information request asking the Applicant to resubmit the protocol concept sheet for Study 2 as an amendment to supplement STN 125752/276 for review with the following revised milestones schedule:

Study Start Date: November 30, 2025
Interim Analysis Date: May 31, 2026
Study Completion Date: July 31, 2026
Final Report Submission Date: January 31, 2027
Benefit-Risk Assessment Submission: May 31, 2027

The Applicant's proposal for Study 2 was consistent with CBER OCD's request as detailed in the Center Director Decisional Memo for STN 125752/276 dated July 9, 2025, and was designated as PMC #1 in the July 9, 2025, approval letter for STN 125752/276.

On August 22, 2025, CBER issued an information request asking the Applicant to confirm the updated milestone dates for Study 1. The Applicant responded on August 22, 2025, in amendment 15 to STN 125752/305, providing revised milestone dates based on the current status of their mRNA-1273-P403 Subprotocol 03 study. These dates were reviewed by CBER OCD and determined to be acceptable.

Below are the agreed upon Section 506B PMCs and their corresponding milestones for STN 125752/305, as requested by the CBER OCD, which were included in the August 27, 2025, approval letter:

1. Study mRNA-1273-P403 Subprotocol 03: A Phase 3b/4, Open-label, Single Arm Study to Evaluate the Immunogenicity and Safety of mRNA-1273.251 in Individuals ≥65 Years and ≥12 to <65 Years with Risk Factors for Severe COVID-19

   Final Protocol Submission: 20 June 2025 (Completed)
   Study Initiation: 21 July 2025 (Completed)
   Protocol Amendment Submission: 30 September 2025
   Part A Data Memo: 31 December 2025
   Part B Interim Results: 30 April 2026
   Study Completion: 31 May 2026
   Final Report Submission: 31 October 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: 30 November 2025
   Study Completion: 31 January 2027
   Final Report Submission: 31 January 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 postvaccination.

For Scientific and Regulatory Rationale (as per CBER SOPP 8415) for requesting the above PMCs - please refer to the Center Director Decisional Memos dated August 26,

2025 (STN 125752/305) and July 9, 2025 (STN 125752/276) (https://www.fda.gov/media/187542/download?attachment).

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 125752/305 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.