CENTER DIRECTOR OVERRIDE MEMO

May 30, 2025

BLA:	STN 125835/0
Product Name:	MNEXSPIKE (COVID-19 Vaccine, mRNA)
Indication:	Indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). MNEXSPIKE is approved for use 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.
Applicant:	ModernaTX, Inc.
Author:	Vinayak Prasad, M.D., MPH., Director, Center for Biologics Evaluation and Research (CBER), FDA

Summary

This memorandum explains CBER's decision on the above submission. I have read the reviews and recommendations of the BLA review team. In addition to those I have read and reviewed pertinent portions of the sponsor's submission, as well as research on this topic in the peer reviewed literature.

The review team has done a commendable job in summarizing and analyzing the submission to date. Nevertheless, I disagree with certain aspects of their conclusions and instead reach the conclusion described below.

The decision to approve the Biologics License Application (BLA) for MNEXSPIKE is for the following indication: for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for use in individuals who have been previously vaccinated with any COVID-19 vaccine and are: (1) 65 years of age and older or (2) 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. Moreover, the company has agreed to a post-marketing commitment (PMC) to assess the efficacy of the product among 50- to 64-year-old individuals in a randomized controlled trial. I concur with this approval and reach my decision based on the considerations outlined below.

Discussion

Reference is made to ModernaTx, Inc.'s original BLA (STN 125835/0) received on September 30, 2024, and subsequent amendments received on or before May 30, 2025, through which ModernaTx, Inc. (Applicant) sought traditional approval of COVID-19 Vaccine, mRNA (MNEXSPIKE) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 12 years of age and older. CBER's OCD has concluded, for the reasons outlined below, that the BLA be limited to the following individuals at high risk of severe COVID-19 outcomes: those age 65 and older and those from 12 years through 64 years of age with at least one high risk feature listed by the Centers for Disease Control and Prevention (CDC).[1] The Applicant submitted an amendment to the BLA revising their product labeling to align with this indication on May 28, 2025. The applicant's proposed changes are acceptable.

There are multiple reasons why CBER has decided to limit the approval to individuals who are 65 years of age or older or at high risk of severe outcomes from COVID-19.

First, the estimated efficacy of the vaccine is based primarily on a phase 3 randomized clinical trial of individuals ages 12 and older assessing noninferiority to the mRNA-1273 original Omicron BA.4/BA.5 vaccine (Study 1). This study found noninferior vaccine efficacy and neutralizing antibody titers of mRNA-1283 MNEXSPIKE (mRNA-1283) compared with SPIKEVAX (mRNA-1273). However, it is unclear what the efficacy of the mRNA-1273 original Omicron BA.4/BA.5 vaccine was at the time the study was conducted because 1) The BA.4 and BA.5 variants were no longer dominant during the study period and 2) The efficacy of mRNA-1273 against Omicron subvariants and among those with prior immunity has not been established with randomized placebo controlled trials but is based on immunogenicity data and observational or real world data.

We note that the sponsor has provided randomized immunogenicity data targeting the XBB variant (Study 2). However, our ability to estimate clinical efficacy against novel COVID-19 variants from these types of studies is limited because the amount of protection conferred by an increase in neutralizing antibodies is unclear.[2] A 2025 observational study found antibody response to be significantly correlated with protection against self-reported repeat infection.[3] Although individuals with the highest neutralizing antibodies titers were found to have fewer

[1] https://www.cdc.gov/covid/risk-factors/index.html

[2] Zhang, B., Fong, Y., Fintzi, J. et al. Omicron COVID-19 immune correlates analysis of a third dose of mRNA-1273 in the COVE trial. Nat Commun 15, 7954 (2024). Zhang, B., Fong, Y., Fintzi, J. et al. Omicron COVID-19 immune correlates analysis of a third dose of mRNA-1273 in the COVE trial. Nat Commun 15, 7954 (2024).

[3] Zhang B, Fong Y, Coronavirus Variant Immunologic Landscape Trial (COVAIL) Study Team. Neutralizing antibody immune correlates in COVAIL trial recipients of an mRNA second COVID-19 vaccine boost. Nat Commun. 2025 Jan 17;16(1):759.

repeat infections, it is unclear if the protection stemmed from factors innate to these individuals rather than from the absolute quantity of antibodies. Protection against future severe COVID-19 may predominantly come from other facets of the immune system, such as innate immunity or cell mediated immunity.[4,5] A causal relationship between a rise in neutralizing antibody titers and a diminished risk of severe COVID-19 outcomes has not been established, nor has the precise strength of such a relationship. For this reason, I feel there is uncertainty regarding the clinical efficacy of MNEXSPIKE.

In terms of safety, despite the totality of data presented in the BLA, I am unable to conclude that the product has improved safety or reduced reactogenicity for younger individuals at low risk of severe disease. Furthermore, uncommon risks, including those that might be novel to MNEXSPIKE, cannot be ruled out as the largest MNEXSPIKE trial remains limited by including only 5,706 vaccinated participants. Furthermore, rates and long-term sequelae of myocarditis in the highest risk group (adolescent and young adult males) following vaccination with MNEXSPIKE cannot be precisely ascertained from the data provided. For this reason, FDA has instructed the sponsor to update the package insert to reflect what is currently known about myocarditis risks following the mRNA-1273 vaccine.

The risk of severe outcomes from COVID-19 has decreased dramatically over the last four years.[6,7] The infection fatality rate is estimated to have decreased approximately 10-fold with the emergence of the Omicron subvariants coupled with increased prior immunity rates.[6] Therefore, individuals who were previously at low risk of severe outcomes from COVID-19 now have even lower risks of death, hospitalization and severe disease due to COVID-19. Already as of 2022, the infection fatality rate among adults <73 years old without medical comorbidities was estimated to be under 0.007%.[8] Cumulative 2024-2025 COVID-19 hospitalization rates in the United States were lower than the 2024-2025 influenza season.[9]

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[4] Zhang B, Fong Y, Coronavirus Variant Immunologic Landscape Trial (COVAIL) Study Team. Neutralizing antibody immune correlates in COVAIL trial recipients of an mRNA second COVID-19 vaccine boost. Nat Commun. 2025 Jan 17;16(1):759.

[5] Wang L, Nicols A, Turtle L, Richter A, Duncan CJ, Dunachie SJ, Klenerman P, Payne RP. T cell immune memory after covid-19 and vaccination. BMJ Med. 2023 Nov 22;2(1):e000468.

[6] Riedmann U, Chalupka A, Richter L, Sprenger M, Rauch W, Krause R, Willeit P, Schennach H, Benka B, Werber D, Høeg TB, Ioannidis JP, Pilz S. COVID-19 case fatality rate and infection fatality rate from 2020 to 2023: Nationwide analysis in Austria. J Infect Public Health. 2025 Apr;18(4):102698

[7] Erikstrup C, Laksafoss AD, et al. Seroprevalence and infection fatality rate of the SARS-CoV-2 Omicron variant in Denmark: A nationwide serosurveillance study. Lancet Reg Health Eur. 2022 Oct;21:100479.

[8] Erikstrup C, Laksafoss AD, et al. Seroprevalence and infection fatality rate of the SARS-CoV-2 Omicron variant in Denmark: A nationwide serosurveillance study. Lancet Reg Health Eur. 2022 Oct;21:100479. doi: 10.1016/j.lanepe.2022.100479. Epub 2022 Aug 5.

[9] https://www.cdc.gov/resp-net/dashboard/index.html

Due to the decrease in disease severity, vaccination-related harms have potential of outweighing potential benefits in low-risk populations. Some risk-benefit analyses of mRNA vaccines suggested net harm of ongoing vaccination of low-risk populations.[24,25] Although the FDA monitors the safety of all vaccines through post-market surveillance, it is important to acknowledge circumstances in which the potential for benefit from vaccination among non-high-risk individuals is small and poorly defined. Ultimately, only large, randomized studies can provide clarity for low-risk populations.

To further address the unclear current efficacy of Moderna mRNA-1273, the sponsor's randomized clinical trials of COVID-19 vaccines performed in 2020 and 2021 demonstrated acceptable efficacy against symptomatic COVID-19. However, subsequent efficacy assessments for updated vaccine formulations against Omicron subvariants have been based on immunogenicity data and observational data or real-world data. The results of the initial clinical trials do not necessarily apply to today's circumstances with widespread population immunity and in the setting of the currently circulating omicron subvariants.

FDA's regulatory approach for updated formulations of the SARS-CoV-2 vaccines has been similar to FDA's historical approach to updated yearly influenza vaccines. Yet, the SARS-CoV-2 virus and the influenza virus differ in important ways. First, infection with the SARS-CoV-2 virus has been shown to provide durable protection against future severe disease and death, which appears to extend beyond protection conferred by vaccination.[10] Second, the rate of viral evolution of SARS-CoV-2 is markedly slower than influenza. One analysis estimated SARS-CoV-2 has a replication rate 24-fold lower than influenza.[11] This slower rate of evolution is reflected in both the 2025 World Health Organization's and the Vaccines and Related Biological Products Advisory Committee's analysis and recommendation that the upcoming 2025-2026 COVID-19 vaccine formulations should continue to target the JN.1 lineage.[12,13] The slower rate of viral evolution of SARS-CoV-2 is also consistent with the more robust protection against severe COVID-19 observed in subsequent seasons following prior infection[14] which may be mediated by cellular immunity[15] and is seen to a much lesser extent with the influenza virus.[16]

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[10] COVID-19 Forecasting Team. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. Lancet. 2023 Mar 11;401(10379):833-842.

[11] Kawasaki Y, Abe H, Yasuda J. Comparison of genome replication fidelity between SARS-CoV-2 and influenza A virus in cell culture. Sci Rep. 2023 Aug 11;13(1):13105.

[12] https://www.who.int/news/item/15-05-2025-statement-on-the-antigen-composition-of-covid-19-vaccines#:~:text=As%20of%20May%202025%2C%20currently,to%20GISAID%20continues%20to%20increase

[13] COVID-19 Vaccines (2025-2026 Formula) for Use in the United States Beginning in Fall 2025 | FDA

[14] COVID-19 Forecasting Team. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. Lancet. 2023 Mar 11;401(10379):833-842.

[15] Wang L, Nicols A, Turtle L, Richter A, Duncan CJ, Dunachie SJ, Klenerman P, Payne RP. T cell immune memory after covid-19 and vaccination. BMJ Med. 2023 Nov 22;2(1):e000468

[16] Patel MM, York IA, Monto AS, Thompson MG, Fry AM. Immune-mediated attenuation of influenza illness after infection: opportunities and challenges. Lancet Microbe. 2021 Dec;2(12):e715-e725.

Observational data, which has generally been supportive of risk reduction from additional vaccine doses, is subject to multiple categories of bias, including, but not limited to the healthy vaccinee bias, which limits our ability to draw conclusions about vaccine efficacy. This bias is rooted in the fact that individuals seeking additional doses have different demographic characteristics, risk seeking, and health affirming behavior than those who do not, precluding reliable causal inference. This bias has been thoroughly documented for the COVID-19 and the influenza vaccine in numerous countries across the world.[17,18,19,20,21] Crucially, this bias was clearly demonstrated in one of the pivotal observational studies utilized to approve the initial COVID-19 booster shots, rendering its conclusions that boosters protected against COVID-19 mortality highly uncertain.[22,17]

The decrease in the chance of developing severe COVID-19, means that the potential for absolute benefit from vaccination has simultaneously decreased. While not a factor in my decision making, it is worth noting that the COVID-19 vaccine schedule of United States diverges from international consensus in recommending annual COVID-19 vaccinations to children and non-high-risk adults under the age of 65.[23,24] This was highlighted at the April 2025 ACIP meeting [23] and discussed in the FDA's recently-announced framework for COVID-19 vaccine approvals, "An Evidence-Based Approach to Covid-19 Vaccination" published in the *New England Journal of Medicine* on May 20th, 2025.[24]

Because the absolute potential for benefit among non-high-risk groups is, at best, marginal and because there is substantial uncertainty about current vaccine efficacy coupled with known serious risks of the mRNA vaccines, For reasons discussed above, CBER OD is approving an indication in a patient population for whom the clinical benefits of ongoing vaccination have a greater potential of outweighing the known and unknown risks, in line with our statutory responsibility and duty. We have also requested and reached concurrence on a PMC study, in which a prospective, randomized, saline placebo-controlled clinical study will be conducted to

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[17] Høeg TB, Duriseti R, Prasad V. Potential "Healthy Vaccinee Bias" in a Study of BNT162b2 Vaccine against Covid-19. N Engl J Med. 2023 Jul 20;389(3):284-285.

[18] Chemaitelly, H et al. Assessing healthy vaccinee effect in COVID-19 vaccine effectiveness studies: A national cohort study in Qatar. medRxiv 2024.07.28.24311115

[19] Riedmann U, Chalupka A, Richter L, Werber D, Sprenger M, Willeit P, Rijksen M, Lodron J, Høeg TB, Ioannidis JP, Pilz S. Underlying health biases in previously-infected SARS-CoV-2 vaccination recipients: A cohort study. J Infect. 2025 Apr 30;90(6):106497.

[20] Fürst T, Bazalová A, Fryčák T, Janošek J. Does the healthy vaccinee bias rule them all? Association of COVID-19 vaccination status and all-cause mortality from an analysis of data from 2.2 million individual health records. Int J Infect Dis. 2024 May;142:106976

[21] Remschmidt, C, Wichmann O, Harder T. Frequency and impact of confounding by indication and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic review. BMC Infect Dis. 2015 Oct 17;15:429.

[22] Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, Yaron S. BNT162b2 Vaccine Booster and Mortality Due to Covid-19. N Engl J Med. 2021 Dec 23;385(26):2413-2420.

[23] https://www.cdc.gov/acip/downloads/slides-2025-04-15-16/05-Panagiotakopoulos-COVID-508.pdf

[24] Prasad V, Makary MA. An Evidence-Based Approach to Covid-19 Vaccination. N Engl J Med. 2025 May 20. doi: 10.1056/NEJMsb2506929

determine if there are additional patient populations for whom a favorable benefit-risk profile exists. The rationale for this study has also been outlined publicly in the aforementioned May 20th, 2025, *New England Journal of Medicine* publication.[25] A successful outcome from the agreed-upon study may be submitted to the BLA to support future labeling changes. The Applicant and CBER OD agree that there is equipoise for such a study in individuals 50 through 64 years of age without risk factors, as illustrated by varying practice patterns among peer nations.[25]

I acknowledge that the USPI includes safety and immunogenicity data in previously-vaccinated individuals 12 years of age and older, with and without high-risk conditions. Although the indication has been revised to exclude some of these individuals, I concur with inclusion of this additional information within the USPI. I believe availability of this additional information will facilitate transparency and ensure that all available safety and immunogenicity data are available to the US public.

Finally, and although this is also not a factor in my decision making, I note that there is emerging consensus in the American medical community with regards to the approach and reasoning presented in this memorandum. On February 25, 2025, former FDA commissioner, Robert Califf, indicated in the *Journal of the American Medical Associatio*n: "Covid vaccine uptake is now low enough that large RCTs are feasible to evaluate the efficacy and safety of new updated boosters."[26] He confirmed this view on May 9th, 2025, on his personal Substack[27] writing: “In the case of COVID-19 I believe it would now be quite reasonable, and even advisable, to conduct placebo-controlled trials for ‘boosters’ using updated versions of the vaccine in people who are not high-risk.”

In light of the considerations detailed here, I have concluded that this application should be approved under section 351(a) of the Public Health Service Act.

[25] Prasad V, Makary MA. An Evidence-Based Approach to Covid-19 Vaccination. N Engl J Med. 2025 May 20. doi: 10.1056/NEJMsb2506929.
[26] Consequences and Opportunities From Poor Uptake of COVID Vaccinations Despite Strong Evidence | Medical Education and Training | JAMA | JAMA Network
[27] https://robcaliff272993.substack.com/p/thoughts-on-placebo-controlled-trials