Review Memorandum

Date:	**January 6, 2022**
To:	**The File**
From:	**Peter Marks, MD, PhD (CBER/OD)**
Applicant name:	**ModernaTX, Inc.**
Application Number:	**EUA 27073**
Product:	**Moderna COVID-19 Vaccine**
Subject:	**CBER assessment of a single booster dose of the Moderna COVID-19 Vaccine (0.25 mL) administered at 5 months**

This memorandum provides a summary, review, and recommendation to amend the emergency use authorization (EUA) of the Moderna COVID-19 Vaccine to allow the administration of a single homologous booster dose to individuals 18 years of age or older, at least 5 months after completion of a primary series of the Moderna COVID-19 Vaccine (i.e., as a homologous booster dose), and to authorize use of the Moderna COVID-19 Vaccine as a single booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine (i.e., as a heterologous booster dose) in individuals 18 years of age or older. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

Executive Summary

The Moderna COVID-19 Vaccine's currently authorized indication is for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 18 years of age and older. It is authorized for use as a 2-dose primary series, each dose being 100 µg mRNA (0.5 mL), in individuals 18 years of age and older and as a third primary series dose of 100 µg mRNA (0.5 mL) for use in individuals 18 years of age and older with certain immunocompromising conditions. A single booster dose of 50 µg mRNA (0.25 mL) of the Moderna COVID-19 Vaccine is authorized for use in individuals 18 years of age and older following completion of a primary series of the Moderna COVID-19 Vaccine (homologous booster) or for those 18 years of age and older following completion of primary vaccination with another FDA-authorized COVID-19 vaccine (heterologous booster). The authorized interval between completion of primary vaccination and booster dose for a Moderna COVID-19 Vaccine homologous booster is currently at least 6 months, and for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

On December 1, 2021, the first confirmed case of the SARS-CoV-2 variant Omicron (B.1.1.529) was identified in the United States. Since that time, the proportion of cases due to the Omicron variant is estimated to have increased to be over 50% and is rising. This rapid increase in the proportion of cases

attributable to the Omicron variant, relative to the previously highly prevalent SARS-CoV-2 variant Delta (B.1.617.2), is contemporaneous with a surge in COVID-19 cases in the United States. Laboratory data indicate that the Omicron variant is more resistant to neutralization by the antibodies generated with the currently available COVID-19 vaccines, and that a third mRNA vaccine dose may provide improved protection against the Omicron variant. In this context, the current action allows the administration of a single homologous booster dose of the Moderna COVID-19 Vaccine (to individuals 18 years of age and older at least 5 months after completion of a primary series. A single 50 µg booster dose of the Moderna COVID-19 Vaccine (0.25 mL) may be administered to individuals 18 years of age and older as a heterologous booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine. [1] The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

Data previously provided by the sponsor indicated that a 50 µg (0.25 mL) booster dose of the Moderna COVID-19 Vaccine administered to individuals 18 years of age and older at least 6 months following completion of a 2-dose primary series resulted in a neutralizing antibody geometric mean titer ratio of 1.8-fold for the geometric mean titer one month after the booster dose relative to the geometric mean titer one month after completion of the primary series. Additional immunogenicity data supported activity of neutralizing antibodies elicited by the vaccine against the SARS-CoV-2 Delta variant.

Data reviewed in support of the current action include information provided by the sponsor in its request submitted on January 4, 2022, that following a booster dose of their vaccine administered after the 2-dose primary series, neutralization capacity for the Omicron variant is reduced by half in 57 days. The sponsor also references a study conducted by the National Institute of Allergy and Infectious Disease in a total of 154 individuals who received a 100 µg booster dose between 12.0 and 20.9 weeks following completion of the primary series of either Moderna, Pfizer-BioNTech, or Janssen COVID-19 vaccines with good immunogenicity and no observed safety concerns. Though obtained with a different mRNA vaccine, additional relevant data reviewed by the agency includes that from the Ministry of Health of Israel indicating no new safety concerns in 4.1 million individuals age 16 years and older who received the Pfizer-BioNTech COVID-19 Vaccine series with booster doses administered at least 5 months following completion of the primary series. Although the overall composition of the Moderna COVID-19 Vaccine is different than the Pfizer-BioNTech COVID-19 Vaccine, both are mRNA vaccines with safety and efficacy profiles that, though not identical, are relatively similar. Acknowledging the differences, it is reasonable to make the inference that the safety data on the 5 month interval for booster doses obtained in the population in Israel can apply to the Moderna COVID-19 Vaccine.

Based on an assessment of benefits and risks informed by available data, FDA has concluded that the data support the administration of a single homologous booster dose of 50 µg (0.25 mL) of the Moderna COVID-19 Vaccine to individuals 18 years of age or older, at least 5 months after completion of a primary series of this vaccine (i.e., as a homologous booster dose), and to authorize use of the vaccine as a single booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine (i.e., as a heterologous booster dose) in individuals 18 years of age or older. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination..

Review

Disease Background

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus). SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV). SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of January 4, 2022, has caused approximately 282 million cases of COVID-19, including over 5.4 million deaths worldwide. In the United States, more than 53.7 million cases and 820,000 deaths have been reported to the Centers for Disease Control and Prevention (CDC). While the pandemic has caused morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2, and emerging variants (such as the very highly transmissible Omicron variant that is now rapidly spreading and predominant in the United States) have caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education).

Following EUA of COVID-19 vaccines in December 2020, COVID-19 cases and deaths in the United States declined sharply during the first half of 2021. The emergence of the Delta (B.1.617.2) and Omicron (B.1.1.529) variants and their rapid spread across the globe, variable implementation of public health measures designed to control spread, and continued transmission among unvaccinated individuals are major factors in the recent resurgence of COVID-19. Although the number of COVID-19 cases appeared to be declining in October 2021 relative to the Delta variant-associated peak globally and in the United States, during the months of November and December 2021 there was a marked increase in cases in Western Europe and the number of cases in the United States increased starting in early November 2021.

Of particular concern, the Omicron variant was initially identified in the Republic of South Africa in November 2021, with subsequent detection worldwide. On December 1, 2021, the first confirmed case of the Omicron variant was identified in the United States. Since that time, the proportion of cases due to the Omicron variant in the United States is estimated to be over 50% of the COVID-19 cases and appears to be increasing (https://covid.cdc.gov/covid-data-tracker/#variant-proportions). This rapid increase in the proportion of cases attributable to the Omicron variant, relative to the previously highly prevalent Delta variant, is contemporaneous with a surge in COVID-19 cases in the United States.

Although data continue to emerge on a daily basis, the full significance of the Omicron variant has recently become more clear. This variant appears to be highly transmissible, with a reproductive number that appears to be several times higher than that for the Delta variant (Nishiura H, Ito K, Anzai A, et al., Relative reproductive number of SARS-CoV-2 Omicron (B.1.1.529) compared with Delta variant in South

Africa, J Clin Med, 2022; 11:30). Additionally, both laboratory and clinical data indicate that the Omicron variant appears to be significantly more resistant to neutralization by antibodies developed to the prototype Wuhan strain of SARS-CoV-2, and this variant has been associated with breakthrough infections even in fully vaccinated individuals (Cao Y, Wang J, Jian F, et al. Omicron escapes the majority of existing SARS CoV-2 neutralizing antibodies, Nature 2021, in press, https://doi.org/10.1038/d41586-02103796-6; Branal LT, MacDonald E, Veneti L et al., Outbreak caused by the SARS-CoV-2 Omicron variant in Norway, November to December 2021, Euro Surveill, 2021, https://doi.org/10.2807/1560-7917.ES.2021.26.50.2101147). Based on the available evidence, it appears that the primary series of the COVID-19 vaccines currently available in the United States does reduce the risk of serious disease, including hospitalization and death, from the Omicron variant, and the recent administration of a booster dose of a COVID-19 vaccine appears to be associated with an even lower likelihood of breakthrough infection.

The Moderna COVID-19 Vaccine for the Prevention of COVID-19

On December 18, 2020, FDA issued an EUA for the Moderna COVID-19 Vaccine (also known as mRNA-1273), for active immunization to prevent COVID-19 due to SARS-CoV-2 in individuals 18 years of age and older. The vaccine is based on the SARS-CoV-2 spike glycoprotein antigen encoded by modified mRNA and formulated in lipid particles. The authorized regimen is a 2-dose primary vaccination series administered 1 month apart, with each dose (0.5 mL) containing 100 µg mRNA. Issuance of the EUA was based on a finding of vaccine efficacy (VE) of 94.1% compared to placebo against confirmed COVID-19 at least 14 days after completion of the 2-dose vaccination regimen and a favorable benefit/risk balance based on review of the safety data, in a study (P301) of approximately 30,000 participants with a median follow-up of 2 months after completion of the vaccination regimen.

On August 12, 2021, FDA amended the Moderna COVID-19 Vaccine EUA to authorize an additional dose to be given to certain immunocompromised individuals. On October 20, 2021, the FDA amended the Moderna COVID-19 Vaccine EUA to authorize a single booster dose (0.25 mL) containing 50 µg mRNA of the Moderna COVID-19 Vaccine administered at least 6 months after completion of a primary series to individuals 65 years of age and older, individuals 18 through 64 years of age at high risk of severe COVID-19, and individuals 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2.

On November 19, 2021, the FDA amended the Moderna COVID-19 Vaccine to authorize to authorize use of the vaccine as a single booster dose in individuals 18 years of age or older, at least 6 months after completing the primary series of this vaccine (i.e., as a homologous booster dose), and to authorize use of the vaccine as a single booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine (i.e., as a heterologous booster dose) in individuals 18 years of age or older. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

Findings from Post-EUA Surveillance: Myocarditis and Pericarditis

Post-EUA safety surveillance reports received by FDA and CDC identified increased risks of myocarditis and pericarditis, particularly within 7 days following administration of the second dose of a 2-dose primary

series of an mRNA vaccine. Reporting rates for medical chart-confirmed myocarditis and pericarditis in VAERS have been higher among males under 40 years of age than among females and older males and for Moderna COVID-19 Vaccine have been highest in males 18 through 24 years of age (approximately 38.5 cases per million second primary series doses as per CDC presentation to VRBPAC on October 26, 2021). While the rates of myocarditis reported in VAERS following the Moderna COVID-19 Vaccine are similar to those reported following the Pfizer-BioNTech COVID-19 Vaccine in corresponding age groups, some, but not all, observational analyses of postmarketing data suggest that there may be an increased risk of myocarditis and pericarditis in males under 40 years of age following the second dose of the Moderna COVID-19 Vaccine relative to the Pfizer-BioNTech COVID-19 Vaccine (see November 19, 2021 FDA Review Memorandum for additional details). The FDA analyzed data from four administrative claims databases in the Biologics Effectiveness and Safety (BEST) system to estimate the adjusted incidence rate of myocarditis and/or pericarditis per million person-days following receipt of the Moderna COVID-19 Vaccine. For males 18 through 25 years of age, the incidence rate per million person-days within one to seven days after the second dose was 18.26 (95% CI: 9.68–34.46).

Although some cases of vaccine-associated myocarditis and pericarditis have required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals, or whether the vaccine might be associated initially with subclinical myocarditis (and if so, what are the long-term sequelae). A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established. On June 25, 2021, myocarditis and pericarditis were added as important identified risks in the pharmacovigilance plan and included in the Warnings sections of the vaccine Fact Sheets and EUA Prescribing Information. The sponsor is conducting additional post-authorization/post-marketing studies to assess known serious risks of myocarditis and pericarditis as well as to identify an unexpected serious risk of subclinical myocarditis.

The most recent safety data from the Ministry of Health of Israel indicate a rate of myocarditis and pericardits in the overall population of those 16 years of age and older administered the Pfizer-BioNTech COVID-19 Vaccine following a booster dose given at least 5 months following the primary vaccination series that is about 1/3 that of the rate seen following the second vaccine dose. Although the overall composition of the Moderna COVID-19 Vaccine is different than the Pfizer-BioNTech COVID-19 Vaccine, both are mRNA vaccines with safety and efficacy profiles that, though not identical, are relatively similar. Acknowledging the differences between the two different vaccines, it is still reasonable to make the inference that the safety data on the 5 month interval for booster doses obtained in the population in Israel can apply to the Moderna COVID-19 Vaccine.

Need for the Expansion of Booster Doses

Concerns have been raised that declining neutralizing antibody titers or reduced effectiveness against symptomatic disease may herald significant declines in effectiveness against severe disease. The recent emergence of the highly transmissible Delta and Omicron variants of SARS-CoV-2 have resulted in a new wave of COVID-19 cases in many parts of the world and have led to considerations for administration of booster doses to individuals who have already received primary vaccination in an effort to enhance immunity, and thus sustain protection from COVID-19.

In particular, the very large number of recent cases of the Omicron variant is also raising significant concerns, as data indicate that due to the large number of mutations present it escapes neutralization by a variety of monoclonal antibodies and is more resistant to vaccine-induced immunity (Planas D, Saunders N, Maes P, et al., Considerable escape of SARS-CoV-2 Omicron to antibody neutralization, Nature, 2021, in press, https://doi.org/10.1038/d41586-021-03827-2). In this study by Planas and colleagues, a booster dose of the Pfizer-BioNTech COVID-19 Vaccine, as well as primary vaccination of previously infected individuals, strongly increased overall levels of anti-SARS-CoV-2 neutralizing antibodies above a threshold allowing inhibition of the Omicron variant. This finding appears to be relatively robust, as other studies have come to very similar conclusions regarding the potential benefit of a booster dose of the mRNA vaccines (Garcia-Beltran WF, St. Dennis KJ, Hoelzemer A, et al., mRNA-based COVID-19 boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant, Cell, in press, https://doi.org/10.1016/j.cell.2021.12.033; Nemet I, Kliker L, Lustig Y et al., Third BNT162b2 Vaccination Neutralization of SARS-CoV-2 Omicron Infection, N Engl J Med, in press, http://doi.org/10.1056/NEJMc2119358. The totality of available evidence from these and other sources suggests that vaccinated individuals who have completed a primary series and received a subsequent booster with the Pfizer-BioNTech COVID-19 Vaccine are more likely to be better protected against symptomatic infection with the Omicron variant, and especially against severe disease.

Given the potential benefit of a booster dose in providing additional protection against disease due to the rapidly spreading Omicron variant, it is reasonable at this time to expand the use of booster doses to the fullest extent that is scientifically justified.[2] This would include reduction in the booster interval, which for operational efficiency would ideally be aligned between the two authorized or approved mRNA COVID-19 vaccines.

Requirements for EUA

The EUA process allows the Secretary of the United States Department of Health and Human Services (HHS), in appropriate circumstances, to declare that EUAs are justified for products to respond to certain types of threats. On February 4, 2020, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19.[3] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564(b)(1) of the FD&C Act.[4]

Under section 564(c) of the FD&C Act, FDA may issue an EUA during the COVID-19 pandemic after FDA concludes that the following statutory requirements are met:

[2] On January 3, 2022, the EUA of the Pfizer-BioNTech COVID-19 Vaccine was amended to allow the administration of a single homologous booster dose (or heterologous booster dose as authorized for another COVID-19 vaccine) to individuals 18 years of age and older at least 5 months after completion of a primary series of the Pfizer-BioNTech COVID-19 Vaccine

[3] HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.

[4] HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

- The agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.[5]

If these criteria are met, under an EUA, FDA can authorize unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that the known and potential benefits of a booster dose outweigh the known and potential risks.

Data on a Single Booster Dose in Individuals 18 Years and Older

On January 4, 2022, ModernaTX, Inc. submitted a request to reduce the interval for the administration of a booster dose of the Moderna COVID-19 Vaccine from 6 to 5 months following the completion of primary series. Data previously provided by the sponsor indicated that a 50 µg booster dose (0.25 mL) of the Moderna COVID-19 Vaccine administered to individuals 18 years of age and older at least 6 months following completion of a 2-dose primary series resulted in a neutralizing antibody geometric mean titer ratio of 1.8-fold for the geometric mean titer one month after the booster dose relative to the geometric mean titer one month after completion of the primary series. Additional immunogenicity data supported activity of neutralizing antibodies elicited by the vaccine against the SARS-CoV-2 Delta variant.

Data reviewed in support of the current action includes information provided by the sponsor that following a booster dose of their vaccine administered after the 2-dose primary series, neutralization capacity for the Omicron variant is reduced by half in 57 days. The sponsor also references the study conducted by the National Institute of Allergy and Infectious Disease in a total of 154 individuals who received a booster dose of the Moderna vaccine between 12.0 and 20.9 weeks following completion of the primary series of the Moderna, Pfizer-BioNTech or Janssen COVID-19 vaccines with good immunogenicity and no observed safety concerns.

Two publications have documented the effectiveness in a real-world setting of booster doses administered in Israel after at least 5 months after completion of the primary series with the Pfizer-BioNTech COVID-19 Vaccine (Arbel R, Hammerman A, Sergienko R et al., BNT162b2 vaccine booster and mortality due to

[5] Although COMIRNATY is approved to prevent COVID-19 in individuals 16 years of age and older, there are no COVID-19 vaccines that are approved for use in individuals younger than 16 or to provide homologous or heterologous booster doses.

Covid-19, N Engl J Med 2021; 385:2413-20; Bar-On YM, Goldberg Y, Mandel M, et al., Protection against Covid-19 by BNT162b2 booster across age groups, N Engl J Med 2021; 385:2421-30). The most recent safety data available as of December 15, 2021, from the Ministry of Health of Israel based upon over 4.1 million booster doses administered at least 5 months after completion of the primary series indicate a rate of myocarditis and pericardits in the overall population of those 16 years of age and older that is about 1/3 that of the rate seen following the second vaccine dose. Although the overall composition of the Moderna COVID-19 Vaccine is different than the Pfizer-BioNTech COVID-19 vaccine, both are mRNA vaccines with safety and efficacy profiles that, though not identical, are relatively similar. Acknowledging the differences, it is reasonable to make the inference that the safety data on the 5 month interval for booster doses obtained in the population in Israel can apply to the Moderna COVID-19 Vaccine.

Additionally, use of heterologous booster doses with the Moderna COVID-19 Vaccine noted above was previously evaluated and presented at the October 15, 2021 VRBPAC meeting. As noted at the meeting, the median booster interval for the 49 individuals receiving the Moderna COVID-19 Vaccine boosted with the Janssen COVID-19 Vaccine was 19.3 weeks (range 12.6 – 26.0); the median booster interval for the 51 individuals receiving the Moderna COVID-19 Vaccine boosted with the Pfizer-BioNTech COVID-19 Vaccine was 22.9 weeks (range 12.6 – 28.7). The data presented support the authorization of heterologous booster doses of the Janssen or Pfizer COVID-19 vaccine in individuals older than 18 years of age at least 5 months following a primary series of the Moderna COVID-19 Vaccine.

Recommendation

Based on the totality of evidence submitted by the sponsor, the literature, and the Ministry of Health of Israel, and in accordance with established FDA guidance, the review team concludes that the known and potential benefits outweigh the known and potential risks, and therefore recommends the following amendments of the Moderna COVID-19 Vaccine emergency use authorization allowing the administration of a single 50 µg (0.25 mL) homologous booster dose to individuals 18 years of age or older, at least 5 months after completion of a primary series of this vaccine (i.e., as a homologous booster dose), and to authorize use of the vaccine as a single booster dose following completion of primary vaccination with another authorized or approved COVID-19 vaccine (i.e., as a heterologous booster dose) in individuals 18 years of age or older. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination..

Continuous, ongoing safety surveillance under the oversight of FDA and CDC will actively and passively monitor for risks of myocarditis and pericarditis and other known and unknown short and long term risks of the booster doses authorized.