Review Memorandum

Date:	**November 19, 2021**
To:	**The File**
From:	**David Cho, PhD (CBER/OD)**
Through:	**Peter Marks, MD, PhD (CBER/OD)**
Applicant name:	**ModernaTX, Inc.**
Application Number:	**EUA 27073**
Product:	**Moderna COVID-19 Vaccine**
Subject:	**CBER Assessment of a booster dose of Moderna COVID-19 Vaccine (0.25 mL) administered following a primary COVID-19 immunization series in individuals 18 years of age and older**

This memorandum provides a summary, review, and recommendation on the submission by Moderna on November 11, 2021 to amend the emergency use authorization (EUA) of their COVID-19 vaccine to authorize the administration of a booster dose following a primary COVID-19 immunization series to individuals 18 years of age and older.

Executive Summary

Moderna has provided a proposed Amendment to EUA 27073 to include the administration of a booster dose following a primary COVID-19 immunization series to individuals at least 18 years of age. Reference is made to the EUA for Moderna COVID-19 Vaccine issued on December 18, 2020, which describes the safety and effectiveness of this vaccine based on a placebo-controlled randomized trial which had enrolled approximately 30,000 participants. Moderna's current 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 age 18 years and older. On August 12, 2021, the 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 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. Also on October 20, 2021, the FDA authorized the use of a heterologous booster dose for currently available (i.e., FDA-authorized or approved) COVID-19 vaccines. The Moderna COVID-19 booster dose is half of the dose administered for a primary series dose. Based on a revised benefit risk assessment, Moderna requested amendment of the EUA for their COVID-19 vaccine to authorize the administration of a booster dose at least 6 months following a primary COVID-

19 immunization series in individuals at least 18 years of age. Clinical data reviewed by the Agency previously documented that a booster dose of 50 µg administered at least 6 months after a 2-dose Moderna COVID-19 Vaccine primary series was associated with a neutralizing antibody geometric mean titer ratio of 1.8-fold when comparing the geometric mean titer at 4 weeks after a booster dose to the geometric mean titer at 4 weeks after completion of the primary series. Additional data evaluated by FDA included the recent epidemiology of COVID-19 in the United States indicating a widespread increase in the number of cases, as well as real world evidence that suggests by extrapolation that the risk of myocarditis/pericarditis following third doses of the Moderna COVID-19 Vaccine given to 18 to 40 year old males appears to be closer to the risk after the first vaccine dose (i.e., lower than the risk after the second vaccine dose). Based on an assessment of benefits and risks informed by available data, FDA has concluded that the data support the use of booster dose of the Moderna COVID-19 Vaccine following a primary COVID-19 immunization series in all individuals at least 18 years of age.

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 November 17, 2021, has caused approximately 255 million cases of COVID-19, including 5.12 million deaths worldwide. In the United States, more than 47 million cases and 766,000 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 highly transmissible Delta variant that is now predominant in the US) have caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education).

Following emergency use authorization 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 variant, 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 COVID-19 cases appeared to be declining in October 2021 relative to the Delta variant-associated peak globally and in the US, during the month of November 2021 there has been a marked increase in cases in Western Europe and the number of cases in the US has been increasing, rising by about 20% between November 1, 2021, and November 17, 2021. Given the coming winter with more indoor activities due to the cold weather, there is concern that the trend of increasing cases would continue.

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

On December 18, 2020, FDA issued an Emergency Use Authorization 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 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, the 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 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.

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 have been highest in males 12 through 17 years of age (~71.5 cases per million post second primary series doses among males age 16-17 years and 42.6 cases per million post second primary series doses among males age 12-15 years as per CDC presentation to the ACIP on August 30, 2021). In an FDA analysis of the Optum healthcare claims database, the estimated excess risk of myocarditis/pericarditis approached 200 cases per million fully vaccinated males 16-17 years of age and 180 cases per million fully vaccinated males 12-15 years of age. Although some cases of vaccine-associated myocarditis/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. 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 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.

Need for 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 variant of SARS-CoV-2 resulted in a new wave of COVID-19 cases in many parts of the world and has led to considerations for administration of booster doses to individuals who received primary vaccination in an effort to enhance immunity, and thus sustain protection from COVID-19. An increasing body of evidence indicates that while the protection of the Moderna COVID-19 Vaccine remains very strong against the severe forms of COVID-19 that results in hospitalization of death, protection does appear to wane over time. The data indicating waning protection come from a variety of sources and have appeared in the published literature. A study conducted through the Veterans Health Administration showed a similar trend for all three vaccines authorized or approved in the US (https://www.science.org/doi/10.1126/science.abm0620).

Requirements for EUA

Based on the declaration by the Secretary of the US Department of Health and Human Services (HHS) that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)).

- The chemical, biological, radiological, or nuclear (CBRN) 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.[1]

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.

[1] Although COMIRNATY (COVID-19 Vaccine, mRNA) is approved to prevent COVID-19 in individuals 16 years of age and older, there are no COVID-19 vaccines that are approved to provide homologous or heterologous booster doses.

EUA Request

On November 11, 2021, Moderna submitted a request to amend the EUA for its COVID-19 vaccine to authorize the administration of a booster dose at least 6 months following a primary COVID-19 immunization series in individuals at least 18 years of age.

Immunogenicity Data

Reference is made to the Office of Vaccines Research and Review Clinical Review Memo of October 18, 2021, that noted the successful booster dose immunobridging analyses conducted by Moderna. The immunobridging analysis based on neutralizing antibody (ID50) geometric mean titers (GMTs) from Studies P201B and P301 and the robust seroresponse rate from study P201B support inference of effectiveness of the booster dose in individuals 18 years of age and older against the D614G reference strain. Clinical data reviewed by the Agency previously documented that a booster dose of 50 µg administered at least 6 months after a 2-dose Moderna COVID-19 Vaccine primary series was associated with a neutralizing antibody geometric mean titer ratio of 1.8-fold when comparing the geometric mean titer at 4 weeks after a booster dose to the geometric mean titer at 4 weeks after completion of the primary series. Additional exploratory descriptive immunogenicity analyses evaluating neutralization of the Delta variant, although limited by the use of a non-validated assay, support the potential for the booster dose to provide additional protection against the currently circulating Delta variant.

Benefit-Risk

The key benefit of the booster dose of the Moderna COVID-19 Vaccine is to prevent breakthrough COVID-19 cases post-primary series of two doses of COVID-19 vaccine. There is clear evidence that vaccine effectiveness (VE) against SARS-CoV-2 is waning for all adult age groups post-2nd dose of the vaccine.[2] The reduced VE is partially due to the waning of immunity and partially to the emergence of the new Delta variant. Based on safety surveillance, there were no new or significant safety concerns identified after EUA of the booster dose among high-risk populations.

Potential myocarditis risk post-booster dose remains as the key risk in the benefit-risk assessment of the booster dose. There is currently limited data on myocarditis following booster doses of the mRNA vaccines. Real world evidence on the incidence of myocarditis and pericarditis from Israel that has been presented at the Vaccines and Related Biologic Products Advisory Committee (VRBPAC) previously, most

[2] Tartof, Sara Y., et al. "Six-month effectiveness of BNT162B2 mRNA COVID-19 vaccine in a large US Integrated health system: a retrospective cohort study." SSRN, (2021); Barda, Noam, et al. "Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study." The Lancet (2021); Klein N. Myocarditis Analyses in the Vaccine Safety Datalink: Rapid Cycle Analyses and “Head-to-Head” Product Comparisons (presented at Oct 21, 2021 ACIP meeting). Centers for Disease Control and Prevention; October 21, 2021. p. Slide 17. Available at: https://stacks.cdc.gov/view/cdc/110921. Accessed 5 November 2021; Andrews, Nick, et al. "Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK." medRxiv (2021); Levin, Einav G., et al. "Waning immune humoral response to BNT162b2 covid-19 vaccine over 6 months." New England Journal of Medicine (2021).

recently on October 14, 2021, and since updated online (https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_booster-sr-112021.pdf). Extrapolation from data obtained with the Pfizer-BioNTech COVID-19 vaccine (another mRNA vaccine(suggests that the risk of myocarditis for the Moderna COVID-19 Vaccine following a third dose several months following the primary vaccination series is not associated with an unacceptable risk of myocarditis/pericarditis. In particular, rather than being as elevated as following the second dose in males 16-40 years of age, the risk of myocarditis/pericarditis appears to be more similar after the administration of the third dose to the risk observed after the first dose. Further pharmacovigilance will be conducted to more completely address this issue.

Recommendation

Based on the data provided by the sponsor, other data available to FDA including real world evidence, and based upon FDA's benefit-risk analysis, the review team concludes that the data support that the known and potential benefits outweigh the know and potential risks and therefore recommends authorization of the use of booster doses of the Moderna COVID-19 Vaccine following a primary COVID-19 immunization series in all individuals at least 18 years of age.