Review Memorandum

Date:	**March 28, 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 second booster dose of the Moderna COVID-19 Vaccine administered following a first booster dose of any FDA authorized or approved COVID-19 vaccine in certain individuals**

This memorandum provides a summary, review, and recommendation to amend the emergency use authorization (EUA) of the Moderna COVID-19 Vaccine to authorize the administration of a second booster dose, at least 4 months after receipt of a first booster dose of any FDA authorized or approved COVID-19 vaccine, to: individuals 50 years of age and older and individuals 18 years of age and older who have been determined to have certain kinds of immunocompromise.[1]

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 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 at least 5 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, and Omicron and its subvariants are now the predominant circulating

[1] Here, immunocompromise includes those who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

SARS-CoV-2 variants in the United States. The surge in COVID-19 cases since that time has raised concerns about waning protection against COVID-19 and associated serious outcomes among individuals who have received primary vaccination and a single booster dose as currently authorized.

In the current submission, the sponsor has provided information regarding the waning of vaccine protection following a third (first booster) dose of their vaccine and information from an externally conducted, open-label, nonrandomized clinical study evaluating the immunogenicity of a fourth (second booster) dose of their vaccine. The submitted information indicates indirect and limited evidence of clinical benefit from reported immunogenicity findings after a fourth (second booster) dose of Moderna COVID-19 Vaccine.

Subsequent to the submission of the EUA amendment, additional data became available, including studies from the US Centers for Disease Control and Prevention (CDC), the Government of the United Kingdom and from an Israeli health maintenance organization during the Omicron surge. The CDC study provides evidence of lower vaccine effectiveness against hospitalization for a homologous booster dose of the Janssen COVID-19 Vaccine, as compared with a heterologous booster dose of an mRNA COVID-19 vaccine, among individuals who received primary vaccination with the Janssen COVID-19 Vaccine. The study from the United Kingdom provides data to suggest a modest amount of waning of vaccine-induced protection against hospitalization following three mRNA vaccine doses. The Israeli study indicates a potential survival benefit of a fourth (second booster) vaccine dose administered to individuals between 60 and 100 years of age, albeit that the data were analyzed for the effect of a different mRNA vaccine (the Pfizer-BioNTech COVID-19 Vaccine).

Uncertainties associated with the information summarized above include: 1) that some of the information is reported from non-peer-reviewed preprints; 2) that most of the reported experience with waning vaccine effectiveness against COVID-19 associated hospitalization following a first booster dose and additional protection conferred by a second booster dose is from outside the United States; 3) that safety and effectiveness of the Moderna COVID-19 Vaccine second booster dose is inferred in large part by extrapolation from reported evidence following use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 60 years and older; and 4) that the duration of additional protection conferred by a second booster dose is unknown and may be subject to waning, similar to protection conferred by a first booster dose. However, it is reasonable to extrapolate safety and effectiveness conclusions from use of the Pfizer-BioNTech COVID-19 Vaccine as a second booster dose to inform an assessment of benefits and risks for use of the Moderna COVID-19 Vaccine as a second booster dose because both vaccines are mRNA vaccines encoding similar SARS-CoV-2 spike protein antigens, with similar safety and effectiveness reported from studies evaluating these vaccines when used as a first booster dose (homologous or heterologous) in individuals 18 years of age and older. Additionally, in the setting of continued transmission of SARS-CoV-2 (including the BA.2 variant) within communities in the United States, and recent increases in COVID-19 cases reported in Europe and associated with the BA.2 variant, it is reasonable to expect that authorization now of the Moderna COVID-19 Vaccine for use in the United States as a second booster dose would mitigate against increases in COVID-19 hospitalizations and other serious outcomes in the near future among individuals who are at highest risk of these outcomes and who choose to receive a second booster dose.

Additionally, based upon the accumulated experience with primary series and first booster doses (homologous and heterologous) of the Moderna COVID-19 Vaccine, it is also reasonable to extrapolate

experience with a second booster dose in individuals ages 60 years and older (and more limited experience among individuals ages 18-59 years of age) to conclude a favorable benefit-risk balance for use of the Moderna COVID-19 Vaccine as a second booster dose, regardless of the authorized or approved vaccine(s) used for primary series and first booster doses, in adults ages 50-59 years (a group in which the risk of medical comorbidities is elevated compared to adults ages 18-49 years) and in individuals ages 18-49 years with certain kinds of immunocompromise (a group in which the risk of serious outcomes of COVID-19 is elevated compared to the general population).

Therefore, a recommendation is made for the authorization of a second booster dose of the Moderna COVID-19 Vaccine, administered at least four months following the first booster dose, for use in individuals 50 years of age and older and in certain immunocompromised individuals ages 18 years and older. It is also recommended that the authorization be amended to allow a second booster dose of the Moderna COVID-19 Vaccine to be given to those who have received a first booster dose with either the Pfizer-BioNTech COVID-19 Vaccine or the Janssen COVID-19 Vaccine.

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 March 25, 2022, has caused approximately 474.7 million cases of COVID-19, including 6.1 million deaths worldwide. In the United States, more than 79.6 million cases and 972,000 deaths have been reported to the 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 the 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. This variant is highly transmissible, with a reproductive number that is 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). On December 1, 2021, the first confirmed case of the Omicron variant was identified in the United States. The proportion of cases due to the Omicron variant has since eclipsed the Delta variant in the United States. Currently, the Omicron variant is overwhelmingly predominant, with a recent increase in cases due to the BA.2 subvariant. The large peak of COVID-19 cases during the Omicron surge (between December and March, 2022) was associated with an increase in hospitalization and death.

Based on the available evidence, it appears that primary vaccination with any of the COVID-19 vaccines available for use in the United States does reduce the risk of serious disease, including hospitalization and death due to the Omicron variant, and the recent administration of a single booster dose of a COVID-19 vaccine appears to be associated with a notably lower likelihood of breakthrough infection and COVID-19 associated hospitalization compared to primary vaccination alone (Thompon MG, Natarajan K, Irving SA, et al. Effectiveness of a Third Dose of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance – VISION Network, 10 States, August 2021–January 2022, MMWR 2022; 71(4):139–145).

Emerging evidence indicates that there may be some waning of vaccine-induced protection against COVID-19 following a first booster dose of the Pfizer-BioNTech and Moderna COVID-19 vaccines. These data come from the United States, United Kingdom, and Israel. Data from Kaiser Permanente Southern California obtained in a cohort of 14,137 individuals from December 1, 2021 through January 11, 2022, indicate modest waning of vaccine-induced protection against COVID-19, resulting in an approximate 30% increase in urgent care/emergency department visits, and minimal waning against hospitalization (Tartof SY, Slezak, Puzniak, JM, et al. BNT162b2 (Pfizer–BioNTech) mRNA COVID-19 vaccine against omicron-related hospitalization, Lancet, 2022, in press). However, a limitation of this study is that only 26 individuals ages 65 years or older without known immunocompromising conditions were included in the population evaluated.

In a study from the United Kingdom including 409,985 individuals (115,720 cases and 294,265 controls), vaccine effectiveness against hospitalization was 82.4% and 92.4% in those 18 to 64 years of age and 65 years of age and older, respectively, which dropped to 53.6% and 76.9%, respectively, by 15+ weeks after the first booster dose (Stowe J, Andrews N, Kirsebom F, et al., Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation: test negative case-control study, posted on line). The percentage drop was somewhat smaller when only looking at those who required ventilatory support, indicating either that some of these individuals may have been hospitalized with COVID-19 rather than because of complications of COVID-19, or that vaccine effectiveness was more durable against more serious COVID-19 outcomes among hospitalized patients.

Additionally, an observational study from the US CDC VISION network evaluated vaccine effectiveness

against Omicron for a homologous booster dose of Janssen COVID-19 Vaccine, as compared with a heterologous booster dose of an mRNA COVID-19 vaccine, administered after primary vaccination with the Janssen COVID-19 Vaccine (Natarajan K, Prasad N, Dascomb K, Effectiveness of Homologous and Heterologous COVID-19 Booster Doses Following 1 Ad.26.COV2.S (Janssen [Johnson & Johnson]) Vaccine Dose Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults — VISION Network, 10 States, December 2021–March 2022, MMWR, 2022). This study reported that vaccine effectiveness against COVID-19-associated emergency department and urgent care encounters within 7-120 days after the booster dose was 54% for a Janssen COVID-19 Vaccine homologous booster dose and 79% for an mRNA COVID-19 vaccine heterologous booster dose. Vaccine effectiveness against COVID-19-associated hospitalizations within 7-120 days after the booster dose were 67% for a Janssen COVID-19 Vaccine homologous booster dose and 78% for an mRNA COVID-19 vaccine heterologous booster dose.

The totality of evidence reported in the studies noted above suggest that there is a reduction of protection against serious outcomes of COVID-19 following a first mRNA vaccine booster dose and that individuals who received primary vaccination and a homologous booster dose with the Janssen COVD-19 Vaccine may have suboptimal protection against COVID-19 and associated hospitalizations due to the Omicron variant.

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

On January 31, 2022, FDA approved SPIKEVAX made by Moderna Tx, Inc. SPIKEVAX is a vaccine indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The vaccine is administered intramuscularly as a series of two doses (0.5 mL each) 1 month apart, with each dose containing 100 µg messenger RNA (mRNA). SPIKEVAX contains mRNA encoding the SARS-CoV-2 spike glycoprotein antigen of SARS-CoV-2 that is formulated in lipid particles. During clinical development, the vaccine was called mRNA-1273, and the memorandum includes references to this name.

The vaccine is also authorized for use under EUA as the Moderna COVID-19 Vaccine. The EUA for Moderna COVID-19 Vaccine was initially issued on December 18, 2020, for use as a 2-dose primary series in individuals 18 years of age and older. 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 primary series dose to be given to certain immunocompromised individuals 18 years of age and older. 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. Additionally, on October 20, 2021, FDA authorized the use of the Moderna COVID-19 Vaccine as a heterologous booster dose following completion of primary vaccination with currently available (i.e., FDA-authorized) COVID-19 vaccines.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 in individuals 18 years of age or older 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). 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. On January 7, 2022, the EUA was further amended to allow administration of a single booster dose to individuals 18 years of age and older at least 5 months after completion of a primary vaccination series with Moderna COVID-19 Vaccine.

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. 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.

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.[2] 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.[3]

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:

- 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.[4]

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 First and Second Booster Doses of mRNA COVID-19 Vaccines

Evidence considered in support of administration of a second booster dose of the Moderna COVID-19 Vaccine comes both from trials provided by the sponsor and evidence that has appeared in the literature since the sponsor's submission comparing results following the administration of first and second booster doses of mRNA COVID-19 vaccines.

The sponsor provided evidence from an open-label, clinical intervention trial conducted at Sheba Medical Center in Israel of the Moderna COVID-19 Vaccine (mRNA-1273) (Gili Regev-Yochay, Tal Gonen, Mayan Gilboa, et al. Efficacy of a Fourth Dose of Covid-19 mRNA Vaccine against Omicron. NEJM, 2022). A total of 120 participants 18 years of age and older received a fourth (second booster) dose of

[2] 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.
[3] 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.
[4] 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.

mRNA-1273 at least 4 months after the third dose of BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine). The authors reported that after a second booster dose there were approximately 11-fold, 16-fold, and 7-fold increases in geometric mean neutralizing antibody titers against wild-type virus, Delta and Omicron variants, respectively, reported at two weeks after the second booster dose as compared to 5 months after the first booster dose.

The sponsor also provided information from a study conducted by the Israeli Ministry of Health in 1,138,681 people age 60 years or older and in at-risk populations eligible for a fourth dose of an mRNA vaccine. Use of a second booster dose commenced in Israel on January 2, 2022. In this non-peer-reviewed pre-print, the authors reported that administration of a fourth dose (second booster dose) of BNT162b2 at least four months following a third dose (first booster dose) was associated with a 4.3 fold reduction (95% confidence interval (CI), 2.4 to 7.6) in the rate of hospitalization compared to those who had only received three doses (one booster) (Bar-On Y, Goldberg Y, Mandel M, et al., Protection by fourth dose of BNT162b2 against Omicron in Israel, medRxiv). Safety follow-up data available as of March 25, 2022, and reported separately by the Israeli Ministry of Health indicate that there was no increase in the occurrence of myocarditis observed following a second booster dose, and there were no new safety concerns identified.

A study from Israel published as a pre-print after the sponsor's EUA amendment submission included 563,465 individuals between 60 and 100 years of age (some or all potentially overlapping with the Ministry of Health study) including 328,597 (58%) who received a second booster dose of BNT162b2 (Arbel R, Sergienko R, Friger M, et al., Second booster vaccine and Covid-19 mortality in adults 60 to 100 years old, ResearchSquare). In this non-peer-reviewed pre-print, the authors reported that death due to COVID-19 occurred in 92 second-booster recipients and in 232 individuals who received one booster dose indicating an adjusted hazard ratio 0.22 (95% CI 0.17 to 0.28).

The totality of evidence summarized above suggests that a fourth dose (second booster dose) of the Moderna COVID-19 Vaccine, administered at least 4 months after the third dose (first booster dose) of the Moderna COVID-19 Vaccine, would provide additional protection over previous COVID-19 vaccinations in preventing COVID-19 and associated serious outcomes (notably hospitalizations and deaths), with no new safety concerns identified following extensive use of the Pfizer-BioNTech COVID-19 Vaccine as a second booster dose in individuals 60 years of age and older, and that use of the Moderna COVID-19 Vaccine as a second booster dose among individuals in the United States at highest risk of serious complications of COVID-19 could have an appreciable public health impact. Of note, conclusions on known and potential benefits and known and potential risks of a second booster dose of Moderna COVID-19 Vaccine are largely inferred from extrapolation of experience with the Pfizer-BioNTech COVID-19 Vaccine. This inference is based on both vaccines being mRNA vaccines encoding similar SARS-CoV-2 spike protein antigens, with similar safety and effectiveness reported from studies evaluating the two vaccines when used as a first booster dose (homologous or heterologous) in individuals 18 years of age and older (Patel R, Kaki, M, Potluri VS A comprehensive review of SARS-CoV-2 vaccines: Pfizer, Moderna & Johnson & Johnson. Hum Vaccin Immunother. 2022; 18(1): 2002083).

Recommendation

Information submitted with this EUA amendment request and information available from other sources, as summarized in above sections of the review memo, provide evidence suggesting waning (mRNA COVID-19 vaccines) or suboptimal (Janssen COVID-19 Vaccine) protection against COVID-19 and associated serious outcomes following a first booster dose, and direct evidence supporting additional protection and absence of a new safety concern associated with a second booster dose of the Pfizer-BioNTech COVID-19 Vaccine, at least in the short term, among individuals 60 years of age and older. More limited and indirect evidence of potential benefit after a second booster dose of the Moderna COVID-19 Vaccine is provided by immunogenicity findings reported from a study in adults 18 years of age and older.

Uncertainties associated with the information summarized above concerning evidence of waning protection following first booster doses of COVID-19 vaccines and safety and effectiveness of a second booster dose of Moderna COVID-19 Vaccine include: 1) that some of the information is reported from non-peer-reviewed pre-prints; 2) that most of the reported experience with waning vaccine effectiveness against COVID-19 associated hospitalization following a first booster dose and additional protection conferred by a second booster dose is from outside the United States; 3) that safety and effectiveness of the Moderna COVID-19 Vaccine as a second booster dose is inferred in large part by extrapolation from reported evidence following use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 60 years and older; and 4) that the duration of additional protection conferred by a second booster dose is unknown and may be subject to waning similar to protection conferred by a first booser dose. However, as noted above it is reasonable to extrapolate safety and effectiveness conclusions from use of the Pfizer-BioNTech COVID-19 Vaccine as a second booster dose to inform an assessment of benefits and risks for use of the Moderna COVID-19 Vaccine as a second booster dose. Additionally, in the setting of continued transmission of SARS-CoV-2 (including the BA.2 variant) within communities in the United States, and recent increases in COVID-19 cases reported in Europe and associated with the BA.2 variant, it is reasonable to expect that authorization now of the Moderna COVID-19 Vaccine for use in the United States as a second booster dose would mitigate against increases in COVID-19 hospitalizations and other serious outcomes in the near future among individuals who are at highest risk of these outcomes and who choose to receive a second booster dose. Additionally, accumulated experience with primary series and first booster doses (homologous and heterologous[5]) of the Moderna COVID-19 Vaccine provides a reasonable basis to extrapolate experience with a second booster dose in individuals ages 60 years and older (and more limited experience among individuals ages 18-59 years of age) and to conclude a favorable benefit-risk balance for use of the Moderna COVID-19 Vaccine as a second booster dose, regardless of the authorized or approved vaccine(s) used for primary series and first booster doses, in adults ages 50-59 years (a group in which the risk of medical comorbidities is elevated compared to adults ages 18-49 years) and in individuals ages 18-49 years with moderate to severe immunocompromise (a group in which the risk of serious outcomes of COVID-19 is elevated compared to the general population).

[5] Available evidence for use of mRNA-1273 as a first booster dose following the primary series of other FDA-authorized or approved vaccines has supported effectiveness of homologous and heterologous boosting with mRNA-1273 (CBER's review memo dated October 20, 2021, entitled, "EUA amendment to support use of a Moderna COVID-19 Vaccine heterologous booster dose following primary vaccination with other authorized COVID-19 vaccines). Based on this evidence, it is reasonable to extrapolate that mRNA-1273 would be effective as a heterologous second booster dose following a first booster dose with any other authorized or approved COVID-19 vaccine.

Based on the totality of evidence available, including: epidemiology of the modest waning of vaccine-induced protection against serious outcomes of COVID-19 following a third dose of vaccine in the setting of the Omicron variant; continued transmission of SARS-CoV-2, including the BA.2 variant, within communities in the United States; and information provided by the sponsor and available from other sources, the review team concludes that the known and potential benefits of a second booster dose of the Moderna COVID-19 Vaccine, administered at least four months following a first booster of any authorized or approved COVID-19 vaccine to individuals 50 years of age and older and individuals 18 years of age and older with certain kinds of immunocompromise, outweigh the known and potential risks. Therefore, the review team recommends amending the EUA to include use of a second booster dose of the Moderna COVID-19 Vaccine of 50 µg mRNA, at least four months following a first booster dose of any authorized or approved COVID-19 vaccine, in individuals 50 years of age and older and in individuals 18 years of age and older with certain kinds of immunocompromise.

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