Review Memorandum

Date:	**March 28, 2022**
To:	**The File**
From:	**Peter Marks, MD, PhD (CBER/OD)**
Applicant name:	**Pfizer, Inc., on behalf of Pfizer and BioNTech**
Application Number:	**EUA 27034**
Product:	**Pfizer-BioNTech COVID-19 Vaccine**
Subject:	**CBER assessment of a second booster dose of the Pfizer-BioNTech COVID-19 Vaccine (0.3 mL) 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 Pfizer-BioNTech COVID-19 Vaccine to authorize the administration of a second booster dose (0.3 mL), 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 12 years of age and older who have been determined to have certain kinds of immunocompromise.[1]

Executive Summary

The Pfizer-BioNTech 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 5 years of age and older. It is authorized for use as a 2-dose primary series in individuals 5 years of age and older, with a third primary series dose authorized for use in individuals 5 years of age and older with certain immunocompromising conditions. A single booster dose of the Pfizer-BioNTech COVID-19 Vaccine is authorized for use in individuals 12 years of age and older following completion of a primary series of the Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY[2] (homologous booster) or for those 18 years of age and older following completion of primary vaccination with another FDA authorized or approved COVID-19 vaccine (heterologous booster). The authorized interval between completion of primary vaccination and booster dose for a 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.

[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.
[2] COMIRNATY and the Pfizer-BioNTech COVID-19 Vaccine for ages 12 years and older, when prepared according to their respective instructions for use, can be used interchangeably without presenting any safety or effectiveness concerns.

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 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: 1) information regarding the waning of vaccine protection following a third (first booster) dose of their vaccine; 2) information from an externally conducted, open-label, nonrandomized clinical study evaluating the immunogenicity of a fourth (second booster) dose of their vaccine; and 3) real world evidence obtained in Israel shortly after the deployment of a fourth (second booster) dose administered at least four months following a first booster dose. Taken together, the submitted information indicates waning of vaccine-induced protection after the first booster dose against symptomatic disease, more modest waning of protection against hospitalization during the most recent Omicron surge, and additional protection, at least in the short-term, against COVID-19 and COVID-19 associated hospitalization conferred by a fourth (second booster) dose.

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.

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 information is not available for use of the Pfizer-BioNTech COVID-19 Vaccine used as a heterologous second booster dose or used as a second booster dose in individuals younger than 18 years of age; 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, 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 Pfizer-BioNTech 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 Pfizer-BioNTech 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 Pfizer-BioNTech COVID-19 Vaccine as a second booster dose, regardless of the authorized or approved vaccine(s) used for primary vaccination 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 12-49 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 Pfizer-BioNTech 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 12 years and older. It is also recommended that the authorization be amended to allow a second booster dose of the Pfizer-BioNTech COVID-19 Vaccine to be given to those who have received a first booster dose with either the Moderna 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.

COMIRNATY and the Pfizer-BioNTech COVID-19 Vaccine for the Prevention of COVID-19

On August 23, 2021, FDA approved COMIRNATY made by BioNTech in partnership with Pfizer. COMIRNATY is a vaccine indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. The vaccine is administered intramuscularly as a series of two doses (0.3 mL each) 3 weeks apart, with each dose containing 30 µg nucleoside-modified messenger RNA (mRNA). COMIRNATY contains mRNA encoding the viral spike glycoprotein of SARS-CoV-2 that is formulated in lipid particles. During clinical development, the vaccine was called BNT162b2, and the memorandum includes references to this name.

The vaccine is also authorized for use under EUA as the Pfizer-BioNTech COVID-19 Vaccine. The EUA for Pfizer-BioNTech COVID-19 Vaccine was originally issued on December 11, 2020, for use as a 2-dose primary series in individuals 16 years of age and older. Issuance of the EUA was supported by safety and efficacy data from a placebo-controlled randomized trial in >37,000 individuals 16 years of age and older. On May 10, 2021, based on additional clinical trial data that was submitted, the EUA was amended to include adolescents 12 through 15 years of age, using the same dose and dosing regimen as authorized for individuals 16 years of age and older. On August 12, 2021, the EUA was further amended to allow for an additional primary series dose to be given to certain immunocompromised individuals 12 years of age and older. Based on a clinical trial evaluating immunogenicity, FDA amended the EUA on September 22, 2021, to authorize a single booster dose of the Pfizer-BioNTech COVID-19 Vaccine to be administered at least 6 months after completion of a primary series of the Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY 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. Then, on October 20, 2021, FDA authorized the use of the Pfizer-BioNTech COVID-19 Vaccine as a heterologous booster dose following completion of primary vaccination with currently available (i.e., FDA-authorized) COVID-19 vaccines. On October 29, 2021, based on additional clinical trial data, FDA further amended the EUA to authorize use of the Pfizer-BioNTech COVID-19 Vaccine as a

2-dose primary series (each 0.2 mL dose contains 10 µg mRNA) in children 5 through 11 years of age. Then, on November 19, 2021, FDA amended the EUA to includethe use of a single booster dose to include all individuals 18 years of age and older after completion of primary vaccination with Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (homologous booster) or following completion of primary vaccination with another FDA-authorized COVID-19 vaccine (heterologous booster). On December 9, 2021, FDA expanded the use of a single booster dose of Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (homologous booster), six months after completion of primary vaccination with Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY, to individuals 16 to 17 years of age. On January 3, 2022, the EUA was further amended to allow administration of a single booster dose to individuals 12 years of age and older at least 5 months after completion of a primary vaccination series with Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY and to allow a third primary series dose for certain immunocompromised children 5 through 11 years of age.

Findings from Post-EUA Surveillance following Primary Series and First Booster Doses: 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 the Pfizer-BioNTech COVID-19 Vaccine have been highest in males 12 through 17 years of age (~71.5 cases per million second primary series doses among males age 16-17 years and 42.6 cases per million 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 and 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 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.[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:

- 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 First and Second Booster Dose of the Pfizer-BioNTech COVID-19 Vaccine

Evidence considered in support of administration of a second booster dose of the Pfizer-BioNTech 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 (Regev-Yochay G, Gonen T, Gilboa M, et al. 4th dose COVID mRNA vaccines' immunogenicity and efficacy against Omicron VOC, medRxiv). A total of 154 participants 18 years of age and older received a fourth (second booster) dose of BNT162b2 at least 4 months after the third dose. In this non-peer-reviewed pre-print, the authors reported that after a second booster dose there were

[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.
[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.

approximately 11-fold increases in geometric mean neutralizing antibody titers against wild-type virus, Delta and Omicron variants, 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 BNT162b2. 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).

Finally, the sponsor provided information from predictive modeling making the assumption that another wave of COVID-19 might occur with the predicted number of cases that would occur during such a wave derived from the average number of cases between the Alpha, Delta, and Omicron waves. Based on the assumptions used, the sponsor predicted that for every 1,000,000 booster doses administered to individuals 65 years of age and older, that over the course of four months the following would be prevented: 5,112 (range 1,536 to 10,220) symptomatic infections, 1,144 (range 884 to 1,508) hospitalizations, and 468 (range 352 to 612) deaths.

The totality of evidence summarized above suggests that a fourth dose (second booster dose) of BNT162b2, administered at least 4 months after the third dose (first booster dose) of BNT162b2, provides 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, and that use of BNT162b2 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.

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 Pfizer-BioNTech 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 Pfizer-BioNTech 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 information is not available for use of the Pfizer-BioNTech COVID-19 Vaccine used as a heterologous second booster dose or used as a second booster dose in individuals younger than 18 years of age; 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, 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 Pfizer-BioNtech 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)[6] of the Pfizer-BioNTech 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 18-59 years of age) and to conclude a favorable benefit-risk balance for use of the Pfizer-BioNTech 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 12-49 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).

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 Pfizer-BioNTech 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 12 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 Pfizer-BioNTech COVID-19 Vaccine, at least four months following a first booster dose of any

[6] Available evidence for use of BNT162b2 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 BNT162b2 (CBER's review memo dated October 20, 2021, entitled, "EUA amendment to support use of a Pfizer 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 BNT162b2 would be effective as a heterologous second booster dose following a first booster dose with any other authorized or approved COVID-19 vaccine.

authorized or approved COVID-19 vaccine, in individuals 50 years of age and older and in individuals 12 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.