



## **Review Memorandum**

**Date:** November 19, 2021

**To:** The File

**From:** David Cho, PhD (CBER/OD)

**Through:** 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 booster dose of Pfizer-BioNTech COVID-19 Vaccine (0.3 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 Pfizer 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**

Pfizer has provided a proposed Amendment to EUA 27034 to include a booster dose following a primary COVID-19 immunization series in individuals at least 18 years of age. Reference is made to the EUA for Pfizer-BioNTech COVID-19 Vaccine that was issued on December 11, 2020, which describes the safety and efficacy of this vaccine based on 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 expanded to include adolescents 12 through 15 years of age. On August 12, 2021, the EUA was further amended to allow for an additional primary series dose to be given to certain immunocompromised individuals. Comirnaty (COVID-19 Vaccine, mRNA manufactured by Pfizer Inc. for BioNTech Manufacturing GmbH) was licensed for use in individuals 16 years of age and older on August 23, 2021, following submission and review of a biologics license application. Based on a clinical trial evaluating immunogenicity, on September 22, 2021, the FDA amended the EUA 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 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, the FDA authorized the use of a heterologous booster dose for currently available (i.e., FDA-authorized or approved) COVID-19 vaccines. On October

29, 2021, based on additional clinical trial data, the FDA further amended the EUA to authorize use of a Pfizer-BioNTech COVID-19 Vaccine 2-dose primary series in children 5 through 11 years of age. In the October 29, 2021 revision, FDA also authorized a manufacturing change to include an additional formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses tromethamine (Tris) buffer instead of phosphate buffered saline (PBS) used in the originally authorized Pfizer-BioNTech COVID-19 Vaccine.<sup>1</sup> Pfizer-BioNTech'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 age 5 years and older.

The current submission is a request to expand the eligible population for the use of a homologous booster dose to include all individuals 18 years of age and older who have completed a primary series with Pfizer-BioNTech COVID-19 Vaccine or Comirnaty at least 6 months previously. Data reviewed in support of this request included the regulatory submission from Pfizer-BioNTech, data submitted previously by Pfizer-BioNTech to support use of a homologous booster dose under EUA, and real-world data from experience with use of a Pfizer-BioNTech COVID-19 Vaccine booster dose in Israel and the United States.

Data previously provided by the sponsor indicated that booster doses of the Pfizer-BioNTech COVID-19 Vaccine administered after an average of 6 months resulted in a neutralizing antibody geometric mean titer ratio of 3.3-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. The current submission includes data from a clinical trial 10,125 individuals who completed a 2-dose primary series of the Pfizer-BioNTech COVID-19 vaccine and were then randomized to receive a booster dose of the Pfizer-BioNTech COVID-19 Vaccine or placebo; these data have not yet been formally reviewed and verified by the agency. This trial reported restoration of protection against a diagnosis of COVID-19 after a median follow up of 2.5 months to approximately 95%. 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 from Israel and the US indicating the risk of myocarditis/pericarditis following third doses of the Pfizer-BioNTech COVID-19 Vaccine given to 18 to 40 year old males appears to be closer to the risk after the first primary series dose than the risk after the second primary series dose, which is higher. Based on an assessment of benefits and risks informed by available data, FDA has concluded that the data support the use of booster doses of the Pfizer-BioNTech COVID-19 Vaccine following completion of 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

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<sup>1</sup> After the October 29, 2021 revision, Pfizer requested that FDA make a correction for accuracy in the FDA Letter of Authorization (LOA) related to the characterization testing Pfizer had conducted to support the manufacturing change. The Agency agreed that this revision is accurate and has revised the LOA accordingly.

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.

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

On August 23, 2021, FDA approved COMIRNATY (COVID-19 Vaccine, mRNA) made by BioNTech Manufacturing GmbH in partnership with Pfizer, Inc. COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The vaccine is administered IM as a series of two doses (0.3 mL each) 3 weeks apart, with each dose containing 30 µg mRNA. COMIRNATY contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein of SARS-CoV-2 that is formulated in lipid particles. COMIRNATY is the only vaccine or medical product that is FDA approved for prevention of COVID-19. The vaccine known as the Pfizer-BioNTech COVID-19 Vaccine is also authorized under EUA for use as a 2-dose primary series in individuals 12 years of age and older and for use as a third dose of the primary series in individuals 12 years of age and older with certain immunocompromising conditions. A 10 µg dose 2-dose primary series has also been authorized in individuals 5 to 11 years of age. During clinical development, the vaccine was called BNT162b2.

### 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 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/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 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.

### 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 Pfizer-BioNTech COVID-19 Vaccine remains strong against severe COVID-19 that result in hospitalization (according to a recent MMWR report: 93% with 95% confidence interval = 83%–97%, <https://www.cdc.gov/mmwr/volumes/70/wr/mm7042e1.htm>), 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. An Israeli study documented waning of protection that was most notably documented five to six months following primary vaccination for severe disease in individuals over 60 years of age, but which also appeared to extend to less severe disease in younger individuals (<https://www.nejm.org/doi/full/10.1056/NEJMoa2114228>). Another study conducted through the Veterans Health Administration showed 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.<sup>2</sup>

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.

### EUA Request

On November 9, 2021, Pfizer, Inc., on behalf of Pfizer and BioNTech, submitted an EUA request to expand the authorization of the Pfizer-BioNTech COVID-19 Vaccine to authorize administration of a booster dose at 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 September 22, 2021 that noted the successful booster dose immunobridging analyses from the Phase 2/3 portion of study C4591001, which supported inference of effectiveness of the booster dose in individuals 18-55 years of age against the reference strain of SARS-CoV-2 (USA\_WA1/2020). Booster doses of the Pfizer-BioNTech COVID-19 Vaccine administered after an average of 6 months resulted in a neutralizing antibody geometric mean titer ratio of 3.3-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. This review noted that as outlined in the [FDA Guidance document, Emergency Use Authorization for Vaccines to Prevent COVID-19](#), this inference of effectiveness can be extrapolated to other age groups for which the vaccine primary series has been authorized or approved (e.g., individuals >55 years of age). The review also noted that additional exploratory immunogenicity analyses evaluating neutralization of the reference strain and the Delta variant, although limited by small numbers of samples and use of a non-validated assay, supported the potential for the booster dose to provide additional protection against the currently circulating Delta variant.

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<sup>2</sup> 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.

Supportive Data from Randomized Placebo-Controlled Clinical Trial of Boosters

Pfizer-BioNTech conducted a randomized placebo-controlled clinical trial of boosters in 10,125 individuals receiving vaccination with the Pfizer-BioNTech COVID-19 Vaccine or placebo that has not yet been formally reviewed and verified by the agency. Relative vaccine efficacy (RVE) was estimated for booster vaccination with Pfizer-BioNTech COVID-19 Vaccine compared to booster placebo up to the data cutoff date (05 October 2021) during the blinded placebo-controlled follow-up period. The RVE in the evaluable efficacy population without evidence of SARS-CoV-2 infection prior to 7 days post-booster was observed as 95.3% (2-sided 95% CI: 89.5%, 98.3%), based on 6 cases in the BNT162b2 group and 123 cases in the placebo group. Notably, the cases in this booster RVE analysis accrued during a period of July to the October cutoff date, during a time that the highly transmissible Delta variant has been the predominant SARS-CoV-2 strain in circulation.

Benefit-Risk Analysis Based on Updated Analyses

Pfizer included a Benefit Risk analysis as part of the November 9, 2021, EUA request. Summarizing the analysis that the sponsor conducted: predictions per million booster doses administered were calculated using conservative assumptions for hospitalizations. In the table below, which summarizes the data submitted by the sponsor, the lower number indicates no waning of immunity with full protection from hospitalization and the upper number indicates waning of protection with 23 hospitalizations per 100,000.

Table 1. Pfizer Benefit Risk Analysis

<b>Age Range</b>	<b>Age 18-39 years</b>	<b>Age 40-64</b>
SARS-CoV-2 infections prevented	12273-25805	13644-19720
Hospitalizations averted	0-721	0-1797
Excess myocarditis cases	8-9	<2

In reviewing the data submitted, FDA reviewers note that the key benefit of the booster dose of the Pfizer-BioNTech COVID-19 Vaccine is to prevent breakthrough COVID-19 cases post-primary series of two doses of the vaccine. There is clear evidence that vaccine effectiveness (VE) against COVID-19 is waning for all adult age groups post-2nd dose of the vaccine.<sup>3</sup> 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.

<sup>3</sup> 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).

Following submission of the initial benefit-risk assessment on November 9, 2021, which assessed age groups of 18-39 and 40-64 years, submitted a Pfizer submitted a supplemental analysis on November 18, 2021, for males 18-29 years of age in response to a FDA Information Request. To estimate the number of SARS-CoV-2 infections prevented with a booster dose of Pfizer-BioNTech COVID-19 Vaccine, Pfizer's benefit-risk assessment assumed two scenarios: one with disease burden based on the overall average weekly rate of confirmed SARS-CoV-2 infections since the beginning of the pandemic (i.e., an average over all peaks and troughs); and the second based on the peak incidence during the Delta period in the week ending September 11, 2021. Pfizer's benefit-risk assessment assumed VE of two doses prior to a booster was 50% against SARS-CoV-2 infection and 90% after a booster. They assumed the 90% VE was maintained over 6 months. Sponsor also estimated the number of COVID-19-related hospitalizations prevented with a booster of BNT162b2 for two disease burden scenarios described above. They assumed a range of waning VE against hospitalization, from no waning (VE maintained at 90%) to assuming VE after 2 doses waned to 77% against COVID-19-related hospitalization prior to a booster (based on Self et al.<sup>4</sup>) and returned to 90% after a booster was administered. A range of assumed rates of myocarditis were based on data from Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD) in the 7-day risk window after dose 2.

The sponsor's supplemental analysis finds one million booster doses will prevent 16,273 and 25,805 SARS-CoV-2 infections, in the ages 18-39 for the scenarios with average and peak incidence rate, respectively. They find 13,644 and 19,720 prevented SARS-CoV-2 infections per million booster doses for ages 40-64 for the average and peak incidence scenarios, respectively. For the highest risk group (males ages 18-29) prevented SARS-CoV-2 infections range from 12,595 to 17,050 per million booster doses. Sponsor estimated the risk of myocarditis cases per million booster doses based on the myocarditis case rate reported in VAERS and VSD. They estimated myocarditis risk per one million booster doses as 8-9 cases for the 18-39 age group and <2 cases for 40-64 year-olds. This risk increases to 25.4 expected cases in the case of one million males 18-29.

FDA considers the overall approach of Pfizer's benefit-risk assessment sound with the caveat of limited data on the myocarditis rate post booster dose. FDA agrees that the benefits of administering a booster dose to all adults 18 to 64 far outweighed the potential risks given the large number SARS-CoV-2 infections prevented along with the corresponding number of hospitalizations prevented and the small number of myocarditis cases expected. FDA notes that the Benefit-Risk assessment of the Sponsor uses VSD and VAERS data to estimate the myocarditis risk while data from four health claim databases from FDA BEST system (Optum, Healthcore, CVS Health, and Blue Health Intelligence) generated a relatively higher myocarditis case rate. However, this is unlikely to change the benefit-risk balance of the vaccine. Additionally, the Sponsor's estimated waning of VE against COVID-19 cases (50% VE at 6 months post 2nd dose) is greater than FDA's estimates (60-70% at 6 months post 2nd dose) based on CDC vaccine effectiveness study, data from Israel, and other sources of evidence. As a result, benefits may be overestimated in Sponsor's assessment, but again it is unlikely to change the benefit-risk balance.

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<sup>4</sup> Self WH, Tenforde MW, Rhoads JP, et al. Comparative Effectiveness of Moderna, Pfizer- BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions - United States, March-August 2021. *MMWR Morbidity and mortality weekly report* 2021; 70(38): 1337-43.

### Additional Benefit-Risk Considerations

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 recently on October 14, 2021, and since updated on line ([https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files\\_publications\\_corona\\_booster-sr-112021.pdf](https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_booster-sr-112021.pdf)) suggests that the risk of myocarditis for the Pfizer-BioNTech 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 its benefit-risk analysis, the review team concludes that the data support that the known and potential benefits outweigh the known and potential risks and therefore recommends authorization of the use of booster doses of the Pfizer-BioNTech COVID-19 Vaccine following a primary COVID-19 immunization series in all individuals at least 18 years of age.