Emergency Use Authorization (EUA) for an Unapproved Product
Review Memorandum

Identifying Information

Application Type	EUA Amendment
Application Number	EUA 27034, Amendment 645
Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech
Submission Date	September 23, 2022
Receipt Date	September 23, 2022
Signatory Authority	Peter Marks, M.D., Ph.D., Director, CBER
Principal Reviewers	CAPT Michael Smith, Ph.D., Regulatory Project Manager, OVRR/DVRPA Meghan Maguire Thon, Ph.D., Regulatory Project Manager, OVRR/DVRPA Julianne Clifford, Ph.D., Regulatory Project Manager, OVRR/DVRPA Mark Connelly, M.D., Clinical reviewer, OVRR/DVRPA Ye Yang, Ph.D., Biostatistics reviewer, OBPV/DB Xiao Wang, Ph.D., CMC/Product reviewer, OVRR/DVP Kathleen Jones, Ph.D., CMC/Facility reviewer, OCBQ/DMPQ Laura Fontan, B.S., M.B.A., CMC/Facility reviewer, OCBQ/DMPQ Deborah Thompson, M.D., MSPH, PVP reviewer, OBPV/DPV Hong Yang, Ph.D., Benefit-risk assessment reviewer, OBPV/ABRA Osman Yogurtcu, Ph.D., Benefit-risk assessment reviewer, OBPV/ABRA Patrick Funk, Ph.D., Benefit-risk assessment reviewer, OBPV/ABRA Ujwani Nukala, Ph.D., Benefit-risk assessment reviewer, OBPV/ABRA CAPT Oluchi Elekwachi, PharmD, MPH, Labeling reviewer, OCBQ/DCM/APLB
Review Completion Date	October 11, 2022
Established Name/Names used during development	Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
Dosage Forms/Strengths and Route of Administration	A 0.2 mL suspension for intramuscular injection
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Use: A single booster dose administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine
Intended Population	Individuals 5-11 years of age

TABLE OF CONTENTS

1 Executive Summary

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to be an ongoing global health challenge, and as of October 4, 2022, has led to over 618 million cases of coronavirus disease 2019 (COVID-19), including 6.5 million deaths worldwide.[1] The Pfizer-BioNTech COVID-19 Vaccine (also known as BNT162b2) is a nucleoside-modified messenger RNA (mRNA) vaccine encoding the full-length spike (S) protein of the original (ancestral/reference) Wuhan-Hu-1 SARS-CoV-2 strain. The Pfizer-BioNTech COVID-19 Vaccine was initially authorized under Emergency Use Authorization (EUA) on December 10, 2020, for primary series vaccination of individuals 16 years of age and older and subsequently authorized for primary series and booster dose vaccination of individuals 5-11 years of age. The vaccine was also previously authorized for booster vaccination of individuals 12 years of age and older; however, following emergence of the Omicron variant and its sublineages (most recently BA.4/BA.5) and observations of decreased vaccine effectiveness against Omicron sublineages compared to the original strain, formulations of the vaccine containing Omicron components were developed to improve vaccine effectiveness. Following a June 28, 2022, meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) to discuss potential changes to COVID-19 vaccine strain composition for use in future vaccination campaigns and subsequent discussions with World Health Organization (WHO) and other global regulatory authorities, FDA recommended that manufacturers develop bivalent COVID-19 vaccines that include a component based on the original strain and a component based on Omicron BA.4/BA.5 for use as a booster dose potentially beginning in fall 2022. On August 31, 2022, FDA authorized the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use under EUA as a single booster dose in individuals 12 years of age and older, with concurrent revision of the authorization for the original (monovalent) Pfizer-BioNTech COVID-19 Vaccine to no longer include use as a booster dose in individuals 12 years of age and older.

Evidence considered by FDA to support the August 31, 2022, authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) included:

- clinical safety and immunogenicity data in individuals >55 years of age from a study which evaluated a second booster dose of another bivalent vaccine, Bivalent BA.1, which contains original and Omicron BA.1 mRNA components and is manufactured by the same process as the original Pfizer-BioNTech COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5),
- safety and effectiveness data from clinical trials and observational studies which evaluated primary and booster (homologous and heterologous) vaccination with the original Pfizer-BioNTech COVID-19 Vaccine (previously reviewed by FDA),
- post-marketing safety surveillance data with primary series and booster doses of the original Pfizer-BioNTech COVID-19 Vaccine, and
- supportive non-clinical immunogenicity data from a study with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

While clinical data for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are not yet available, FDA determined that for purposes of this EUA it is reasonable to assess the effectiveness and the known and potential benefits and risks of this bivalent vaccine based primarily on extrapolation of data from another bivalent vaccine, Bivalent BA.1, manufactured by the same process and containing original and Omicron BA.1 components, and extensive experience to date with the original Pfizer-BioNTech COVID-19 Vaccine. This

extensive experience with the original vaccine also provides a basis for extrapolation to assess known and potential benefits and risks of the bivalent (Original and Omicron BA.4/BA.5) vaccine as a booster dose administered at least 2 months after completion of primary vaccination or receipt of the most recent booster dose of any authorized or approved monovalent COVID-19 vaccine. Furthermore, this extensive experience with the original Pfizer-BioNTech COVID-19 Vaccine primary series and booster doses supports extrapolation of clinical data with the Bivalent BA.1 vaccine in adults >55 years of age to inform the effectiveness and benefits and risks of the bivalent (Original and Omicron BA.4/BA.5) vaccine for use as a booster dose in younger age groups for whom the original Pfizer-BioNTech COVID-19 Vaccine was previously authorized for use as a booster dose (including individuals 5-11 years of age).

When the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was authorized under EUA on August 31, 2022, for use as a booster dose in individuals 12 years of age and older, manufacturing and product quality information for the presentation intended for use in individuals 5-11 years of age was not yet available. In the current EUA request submission, Pfizer has provided the manufacturing and product quality information needed to support authorization of the presentation intended for use in individuals 5-11 years of age.

Post-marketing safety data for the original Pfizer-BioNTech COVID-19 Vaccine are relevant to the safety evaluation of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) because the vaccines are manufactured using the same process. As of September 21, 2022, more than 364 million doses of the Pfizer-BioNTech COVID-19 Vaccine (including both the original and bivalent formulations) have been administered in the U.S. In recipients of any age and all doses, the most frequently reported preferred terms (PTs) in the Vaccine Adverse Event Reporting System (VAERS) for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent were headache, fatigue, pyrexia, pain, chills, nausea, dizziness, pain in extremity, and injection site pain. For important risks identified in the pharmacovigilance plan for Pfizer-BioNTech COVID-19 Vaccine, anaphylaxis and myocarditis/pericarditis remain identified risks that are included in product labeling. The Sponsor is conducting additional safety-related post-authorization/post-marketing studies for the original Pfizer-BioNTech COVID-19 Vaccine, including post-marketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. The Sponsor will also conduct planned post-authorization studies to evaluate the association between the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and a pre-specified list of AESIs in the general US population.

The totality of scientific evidence available at this time supports the conclusion that a booster dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 5-11 years of age, when administered at least 2 months after either completion of a primary series or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine, may be effective and that the known and potential benefits outweigh the known and potential risks. Therefore, the review team recommends authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) under EUA for use in individuals 5-11 years of age as a single booster dose administered at least 2 months after either completion of a primary series or previous booster dose with an authorized or approved monovalent COVID-19 Vaccine. The review team also recommends a revision to the existing EUA for Pfizer-BioNTech COVID-19 Vaccine to remove the use of the monovalent vaccine as a booster dose in individuals 5-11 years of age.

2 Background

2.1 SARS-CoV-2 Virus and COVID-19

SARS-CoV-2 is a zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with variable respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease while some others, especially those older than 65 years and those with certain co-morbid conditions[2], may develop severe respiratory tract disease including pneumonia and acute severe respiratory distress syndrome, leading to multiorgan failure and death. Most adults with COVID-19 recover within 1 to 2 weeks but symptoms may persist for months in some individuals.[3] Symptoms associated with SARS-CoV-2 infection in individuals less than 18 years of age are similar to those in adults but are generally milder, with fever and cough most commonly reported.[4,5] Other symptoms in children include nausea and vomiting, diarrhea, dyspnea, nasal symptoms, rashes, fatigue and abdominal pain.[4] Most children with COVID-19 recover within 1 to 2 weeks. Estimates of asymptomatic infection in children vary from 15 to 50% of infections.[6,7] However, COVID-19-associated hospitalizations and deaths have occurred in individuals 17 years of age and younger, and for some children, COVID-19 symptoms may continue for weeks to months after their initial illness.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of October 4, 2022, has led to over 618 million cases of COVID-19 and 6.5 million deaths worldwide.[1] In the US, more than 96 million cases and 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).[8] Over 6% of cases occurred in children 5 through 11 years of age.[9]

Since the start of the pandemic caused by the Wuhan-Hu-1 strain of SARS-CoV-2 (also referred to as the ancestral, original, or reference strain), surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors, including but not limited to: emergence of variants with greater transmissibility, greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses. Recent surges, both globally and in the US, have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently Omicron (B.1.1.529). The Omicron variant became the predominant variant circulating in the US in December 2021, and while COVID-19 cases, hospitalizations, and deaths in the US have declined since the peak of the Omicron surge in January 2022, the Omicron variant continues to evolve into sublineages, including the recent BA.4 and BA.5 sublineages, which currently account for nearly all reported COVID-19 cases in the US that have been associated with recent increases in COVID-19 case rates.[10] Population-level evidence suggests an increased reinfection risk associated with the Omicron variant and its sublineages compared to earlier SARS-CoV-2 variants.[11] Additionally, available evidence demonstrates waning of immunity elicited by COVID-19 primary vaccination and booster doses and reduced effectiveness of currently available vaccines based on the original SARS-CoV-2 strain against COVID-19 caused by the currently dominant Omicron variant sublineages (see Section 3.1 below). Consequently, a booster vaccine that is able to elicit improved protection against the Omicron BA.4/BA.5 sublineages is an important public health need.

Throughout this document, the term “sublineage” indicates the SARS CoV-2 Omicron variant BA.1, BA.4, and/or BA.5 lineage, as specified.

2.2 Authorized and Approved Vaccines and Therapies for COVID-19

2.2.1 Comirnaty, Pfizer-BioNTech COVID-19 Vaccine, and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)

Comirnaty (COVID-19 Vaccine, mRNA), manufactured by Pfizer and BioNTech, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Comirnaty contains a nucleoside-modified messenger RNA (mRNA) encoding the S protein of the original SARS-CoV-2 strain that is formulated in lipid particles. Under Emergency Use Authorization (EUA), the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine and is authorized for use as a: three-dose primary series for individuals 6 months through 4 years of age, a two-dose primary series for individuals 5 years of age and older, and a third primary series dose for individuals 5 years of age and older with certain types of immunocompromise. The Pfizer-BioNTech COVID-19 vaccine is also authorized as a first booster dose in individuals 5-11 years of age and older, to be administered at least 5 months after completion of a primary series of the Pfizer-BioNTech COVID-19 Vaccine. A bivalent formulation of the vaccine manufactured using the same process, Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is authorized for use as a single booster dose in individuals 12 years of age and older, to be administered at least 2 months after either completion of primary vaccination or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine. The total mRNA content for each of the authorized and/or approved primary series and booster doses is specified for the age group in which the vaccine is being administered: 3 µg in 0.2 mL (primary series only) for 6 months through 4 years of age, 10 µg in 0.2 mL for 5 through 11 years of age, and 30 µg in 0.3 mL for 12 years of age and older. Safety and effectiveness data supporting approval of Comirnaty and authorization of the Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are detailed in the decision memoranda available on the FDA website.

2.2.2 Spikevax, Moderna COVID-19 Vaccine, and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)

Spikevax (COVID-19 Vaccine, mRNA), manufactured by Moderna, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 18 years of age and older. Spikevax contains nucleoside-modified mRNA that encodes for the full-length spike (S) protein of the original SARS-CoV-2 strain encapsulated in lipid particles. Under EUA, the vaccine is called the Moderna COVID-19 Vaccine and is authorized for use as a: 2-dose primary series for individuals 6 months of age and older, and a third primary series dose for individuals 6 months of age and older with certain types of immunocompromise. A bivalent formulation of the vaccine manufactured using the same process, Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is authorized for use as a single booster dose in individuals 18 years of age and older, to be administered at least 2 months after either completion of primary vaccination or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine. The total mRNA content for each of the authorized and/or approved primary series doses is specified for the age group in which the vaccine is being administered: 25 µg in 0.25 mL for 6 months through 5 years of age, 50 µg in 0.5 mL for 6 through 11 years of age, and 100 µg in 0.5 mL for 12 years old and older. The total mRNA content for the authorized booster dose of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 18 years of age and older is 50 µg in 0.5 mL. Safety and effectiveness data supporting approval of Spikevax and authorization of the Moderna COVID-19 Vaccine are detailed in the decision memoranda available on the FDA website.

2.2.3 Janssen COVID-19 Vaccine

The Janssen COVID-19 Vaccine, a non-replicating adenovirus type 26-vectored vaccine encoding the S protein of SARS-CoV-2 original strain, is authorized for active immunization to prevent COVID-19 in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine. The vaccine is authorized for use in these individuals as a single primary vaccination dose and as a single homologous or heterologous booster dose (the dosing interval for a homologous booster is at least 2 months after the single primary vaccination dose, and the dosing interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination). The safety and effectiveness data supporting authorization for the Janssen COVID-19 Vaccine and limitations on its use are detailed in the decision memoranda available on the FDA website.

2.2.4 Novavax COVID-19 Vaccine

The Novavax COVID-19 Vaccine, Adjuvanted, which contains recombinant S protein of the SARS-CoV-2 original strain and Matrix-M adjuvant, is authorized for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the FDA website.

2.2.5 Therapies for COVID-19

The antiviral Veklury (remdesivir) is currently approved by the FDA for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 testing who are hospitalized, or who are not hospitalized and have mild-to-moderate COVID-19 and are at high risk for severe COVID-19.

Other pharmacological products for pre-exposure prophylaxis of COVID-19, post-exposure prophylaxis and/or treatment of COVID-19 that have received emergency use authorization include the following:

Immune modulators: Baricitinib is authorized for the treatment of COVID-19 in hospitalized patients 2 to less than 18 years of age who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). Tocilizumab is authorized for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

COVID-19 convalescent plasma with high antibody titer is authorized for emergency use as a treatment for COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings.

3 Rationale for Bivalent Booster Doses

3.1 Post-authorization Effectiveness Data Against Clinically Relevant SARS CoV-2 Variants

While the currently authorized and approved COVID-19 vaccines in the US are based on the original SARS-CoV-2 strain, recently and currently circulating SARS-CoV-2 variants harbor

mutations in the S protein that confer at least partial antigenic escape from vaccine-elicited immunity. Nonetheless, currently available vaccines have retained some level of effectiveness against all epidemiologically important SARS-CoV-2 variants that have emerged to date, with higher level effectiveness preserved against more serious outcomes (hospitalization and death) than against mild symptomatic disease.[12,13,14,15,16,17,18,19,20,21,22]

Results from observational studies that have investigated the effectiveness of primary vaccination with authorized and approved vaccines have shown decreased effectiveness against certain variants (notably Omicron, for which neutralizing antibody titers are decreased compared with the original strain) and waning effectiveness over time.[13,14,15] Although first booster doses have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron,[13,14,15,16] observational studies have also indicated waning effectiveness of the first booster dose over time, mainly against mild disease, with some studies also suggesting waning effectiveness against hospitalization[13,17,18,19] and lower effectiveness among the immunocompromised individuals.[20] In Israeli experience with a second booster dose of the Pfizer-BioNTech COVID-19 Vaccine in adults 60 years of age and older, a second booster dose improved VE overall (including a reduction in mortality), although effectiveness against mild disease decreased during a 10-week follow-up period.[21,22]

3.2 June 28th VRBPAC and Subsequent Regulatory Discussions

On June 28, 2022, the 175th meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened in open session to discuss whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines should be modified (see FDA website for background materials). The committee heard presentations on the current epidemiology of the COVID-19 Pandemic and SARS-CoV-2 variants in the United States and COVID-19 vaccine effectiveness (CDC) and future COVID-19 Pandemic epidemiology modeling (J. Lessler, University of North Carolina). In addition, available clinical data on modified COVID-19 vaccines were presented by COVID-19 vaccine manufacturers (Pfizer Inc., ModernaTX, and Novavax Inc.) and considerations for vaccine strain composition from the WHO Technical Advisory Group on COVID-19 Vaccine Composition were also presented (K. Subbarao, WHO). FDA perspective on considerations for strain composition for modifications of COVID-19 vaccines was also provided. After these presentations and committee discussions, the VRBPAC voted 19-2 in favor of the inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the US. Although there was no vote on a more specific strain composition, there was general preference among committee members for a bivalent vaccine with an ancestral strain component and an Omicron variant component and a preference for vaccine coverage of Omicron sublineages BA.4 and BA.5. Several members stressed the need to continue to accumulate additional data on this complex issue.

Following the VRBPAC meeting, FDA and other global regulatory authorities met to discuss preliminary data on adapted vaccines addressing emerging variants and to discuss alignment on the criteria for strain selection and regulatory approaches to address new waves of COVID-19 (see ICMR website for additional details). Based on emerging clinical data, there was a preference for a bivalent vaccine that incorporated a component based on the original strain and an Omicron variant component to provide greater breadth of immunity against SARS-CoV-2 variants including Omicron, as it is currently unknown which strains will be circulating in the future.

On June 30, 2022, FDA notified COVID-19 vaccine manufacturers of a recommendation to develop a bivalent booster vaccine (Original and Omicron BA.4/BA.5) to improve protection

during a potential fall 2022 booster vaccination campaign. FDA requested that sponsors expeditiously begin clinical trials to generate safety and immunogenicity data evaluating a bivalent (Original and Omicron BA.4/BA.5) vaccine in relevant populations. FDA recognized that data in trial participants who would receive the bivalent (Original and Omicron BA.4/BA.5) vaccine would potentially not be available prior to the optimal timeframe for deployment of the vaccine in a potential fall 2022 booster vaccination campaign. Consequently, to address the urgent public health need for COVID-19 vaccine booster doses more closely matched to circulating variants, FDA considered that it may be appropriate to issue an Emergency Use Authorization of a bivalent (Original and Omicron BA.4/BA.5) vaccine based primarily on relevant safety and effectiveness data from participants who received an earlier bivalent vaccine (Original and Omicron BA.1), plus supportive pre-clinical animal data for the recommended bivalent vaccine (Original and Omicron BA.4/BA.5), as well as data from use of already-authorized vaccines. Section 5.2 of this memo provides FDA considerations for this approach, which underlay EUA of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) on August 31, 2022, for use as a single booster dose in individuals 12 years of age and older.

4 Regulatory Considerations for an Omicron Booster EUA

4.1 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of the U.S. 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.

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 a vaccine's known and potential benefits outweigh its known and potential risks. This includes demonstrating that manufacturing information ensures product quality and consistency.

4.2 FDA Guidance for Industry Related to COVID-19 Vaccines, Including Modified COVID-19 Vaccines

Appendix 2 of the FDA Guidance for Industry, Emergency Use Authorization for Vaccines to Prevent COVID-19 (originally issued in October 2020 and last updated March 2022) discusses an approach to CMC, nonclinical and clinical data to support the safety and effectiveness of a modified vaccine to address emerging SARS-CoV-2 variants. Although the approach outlined in Appendix 2 does not specifically address considerations for multivalent modified vaccines, the approach and associated immunogenicity endpoints and analyses for supporting vaccine effectiveness are relevant to bivalent modified vaccines. In discussions with COVID-19 vaccine manufacturers, FDA has advised that effectiveness of a bivalent (original and Omicron variant) vaccine should be supported by immunobridging analyses demonstrating: 1) statistically superior neutralizing geometric mean titers (GMTs) against the Omicron variant elicited by the bivalent vaccine as compared to the previously authorized original vaccine; 2) statistically non-inferior neutralizing antibody seroresponse rates against the Omicron variant elicited by the bivalent vaccine as compared to the previously authorized original vaccine; 3) statistically non-inferior neutralizing antibody GMTs against the original strain elicited by the bivalent vaccine as compared to the previously authorized original vaccine; and 4) statistically non-inferior neutralizing antibody seroresponse rates against the original strain elicited by the bivalent vaccine as compared to the previously authorized original vaccine. FDA also advised vaccine manufacturers that, as discussed in the guidance document for monovalent modified vaccines, safety data to support EUA of a modified bivalent vaccine should include analyses of adverse events collected during the immunogenicity evaluation period. While the guidance encouraged clinical evaluation of modified vaccines across different age groups, the guidance also indicates that extrapolation of data accrued in one age group to support EUA of a modified vaccine in other age groups could be considered.

5 EUA Amendment Request for the Bivalent Pfizer-BioNTech COVID-19 Vaccine Booster Dose for Individuals 5-11 Years of Age

5.1 Summary of the EUA Request

On September 23, 2022, Pfizer and BioNTech submitted a request to amend the EUA to include use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 5-11 years of age as a single booster dose after either completion of primary vaccination or receipt of the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. Each 10 µg dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is formulated to contain 5 µg of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of the original SARS-CoV-2 strain and 5 µg of modRNA encoding the S glycoprotein of SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). The S-proteins of the SARS- CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.

The EUA amendment request is based on: extrapolation of clinical trial data that supported the previous authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA/5) for use in individuals 12 years of age and older; clinical trial data and post-authorization experience with the original (monovalent) Pfizer-BioNTech COVID-19 Vaccine used as a primary series and booster dose in individuals 5-11 years of age; and product quality and manufacturing information for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA/5) presentation intended for use in individuals 5-11 years of age).

5.2 FDA Approach to Extrapolation from Available Clinical Data

Due to the rapid evolution of SARS-CoV-2 virus variants, including the currently predominant circulating Omicron sublineages, improved protection for the upcoming winter season could be achieved with expedient authorization and deployment of modified COVID-19 vaccines, for use as booster doses, that are more closely antigenically matched to currently circulating SARS-CoV-2 than the currently authorized COVID-19 vaccines. The Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was authorized under EUA for use as a booster dose in individuals 12 years of age and older based on the totality of evidence, as summarized below and reviewed in detail in the August 31, 2022 FDA Decision Memorandum, indicating that an improved booster dose antibody response to SARS-CoV-2 Omicron sublineages, and therefore the potential for improved vaccine effectiveness results from inclusion of an Omicron component in the vaccine, together with the original (ancestral/reference) component, as a bivalent formulation.

Authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was based on extrapolation of available immunogenicity and safety data from a clinical trial that evaluated the Bivalent BA.1 (Original and Omicron BA.1) vaccine formulation in 610 individuals >55 years of age who received the bivalent vaccine (N=305) or original (monovalent) vaccine (N=305) as a second booster dose and who were followed for a median of 1.7 and 1.8 months, respectively. These data demonstrated that: 1) neutralizing antibody responses against Omicron BA.1 elicited by the Bivalent BA.1 (Original and Omicron BA.1) formulation were statistically superior compared to those elicited by the original (monovalent) BNT162b2 vaccine; 2) neutralizing antibody responses against the reference strain (D614G) elicited by the Bivalent BA.1 (Original and Omicron BA.1) formulation were statistically non-inferior to those elicited by the original (monovalent) BNT162b2 vaccine; and 3) the reactogenicity profile of the bivalent booster dose was similar to that of the original (monovalent) booster dose, and no new safety signals were identified in the clinical trial.

Extrapolation of these data to support authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron) was considered in the context of the totality of available evidence, which included:

- Extensive knowledge of the safety and efficacy of the mRNA COVID-19 vaccine platform;
- Safety, immunogenicity, efficacy, and observational effectiveness data from the original (monovalent) Pfizer-BioNTech COVID-19 Vaccine (BNT162b2); and
- Immunogenicity data from two other modified (monovalent) vaccine candidates manufactured using the same process as BNT162b2 (containing Beta and Omicron BA.1 mRNA components, respectively), which are not reviewed in detail in this memorandum but which, as reported by the Sponsor and as similar to the data for the Bivalent BA.1 (Original and Omicron BA.1) vaccine reviewed in this memorandum, showed statistically significant increases in neutralizing antibody GMTs, as compared to the original BNT162b2 vaccine, to the variant components included in the modified vaccines.

Together, these data informed FDA's assessment of the effectiveness and the known and potential benefits and risks of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

Based upon the accumulated experience with primary series, first booster doses, and second booster doses (homologous and heterologous) of the Pfizer-BioNTech COVID-19 Vaccine, FDA determined that it was reasonable to extrapolate the available safety, efficacy, immunogenicity,

and real-world evidence supporting a favorable benefit-risk balance for first and second booster doses of monovalent (ancestral) mRNA COVID-19 vaccines to conclude a favorable benefit-risk balance for use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as a single booster dose (including for individuals who previously received primary vaccination and two booster doses) at least 2 months after either completion of primary vaccination or the most recent booster dose with any authorized or approved monovalent COVID-19 vaccine. While the available clinical safety and immunogenicity data with the Bivalent BA.1 (Original and Omicron BA.1) booster dose reflected a median interval of 6.3 months (range: 4.7-11.5 months) after the previous COVID-19 vaccine dose, authorization of a minimum interval of 2 months for booster vaccination with Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was also based on extrapolation of data from a published study with BNT162b2 boosters evaluating shorter intervals between the primary series and booster doses, along with clinical experience in immunocompromised individuals who received third primary series doses within one to two months of the second primary series dose.[23]

As mentioned in Section 4.2 above, FDA considers that safety and effectiveness data for a bivalent COVID-19 vaccine accrued in a certain age group could be extrapolated to support emergency use authorization in other age groups. Accumulated experience with mRNA COVID-19 vaccines has demonstrated that while some differences in safety profile and magnitude of neutralizing antibody responses are apparent across various age groups, the relationship between safety profile of and neutralizing antibody response to primary series doses as compared to booster doses has been very similar across age groups. FDA therefore considers that it is reasonable to extrapolate safety and effectiveness data for a bivalent COVID-19 vaccine booster dose to any age group for which available evidence has supported (or would support) emergency use authorization of a booster dose of any COVID-19 vaccine manufactured by the same process as the bivalent vaccine. In the case of the Pfizer-BioNTech COVID-19 Vaccine, the monovalent (original) vaccine has been authorized under EUA for use as a booster dose in individuals 5 years of age and older. Thus, FDA considers that it is reasonable to extrapolate safety and effectiveness data with Bivalent BA.1 (Original and Omicron BA.1) accrued in individuals >55 years of age to support EUA of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 5 years of age and older. Manufacturing and product quality information sufficient to support an EUA for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) presentation intended for use in individuals 5 through 11 years of age was previously not available but is now included in the current EUA request submission.

5.3 Basis for EUA Revision to Remove Authorization of the Original Pfizer-BioNTech COVID-19 Vaccine as a Booster Dose

FDA may revise or revoke an EUA if the circumstances justifying its issuance (under section 564(b)(1) of the FD&C Act) no longer exist, the criteria for its issuance are no longer met, or other circumstances make a revision or revocation appropriate to protect the public health or safety (see section 564(g)(2) of the FD&C Act).

Currently, circumstances exist that make it appropriate to revise the Pfizer-BioNTech COVID-19 Vaccine EUA to protect the public health. As outlined in Section 2.2, the monovalent Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) is authorized for use as a 2- or 3-dose primary series (depending on the age group) and as a homologous booster dose in individuals 5-11 years of age. Authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use as a booster dose for use in individuals 5-11 years of age following completion

of primary vaccination or most recent booster dose with any authorized or approved COVID-19 vaccine is being considered for the express purpose of improving protection conferred by COVID-19 booster doses against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit/risk balance for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as compared to BNT162b2. Consequently, at this time, revising the Pfizer-BioNTech COVID-19 Vaccine EUA to remove the authorization of BNT162b2 as booster doses is appropriate to protect the public health.

Accordingly, authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use as a booster dose in individuals 5-11 years of age would be accompanied by the revision of the authorization for the monovalent Pfizer COVID-19 Vaccine (BNT162b2) such that the monovalent vaccine would no longer be authorized for use as a booster dose for use in individuals 5-11 years of age.

6 FDA Review of Post-authorization Safety Data from Booster Doses

As of September 21, 2022, more than 364 million doses of the Pfizer-BioNTech COVID-19 Vaccine (including both the original and bivalent formulations) have been administered in the U.S. Among individuals aged 5-11 years, 11,044,457 individuals have received at least one dose and 1,332,719 individuals have received a first booster dose (CDC COVID Data Tracker, accessed on September 29, 2022). It is not known what proportions of these numbers represent unauthorized use. The Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is currently authorized (as of August 31, 2022) for use as a single booster dose among individuals ages ≥12 years. In addition, post-authorization data for the original Pfizer-BioNTech COVID-19 Vaccine are relevant for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), as these vaccines are manufactured using the same process and both vaccines contain an original SARS-CoV-2 component.

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event (AE) reports following administration of the original Pfizer-BioNTech COVID-19 Vaccine, and the results are briefly summarized below. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was actually due to the vaccine. A 3rd, 4th, or 5th COVID-19 vaccine dose as recorded in VAERS might not represent a dose given as an authorized booster dose.

As of September 27, 2022, among individuals vaccinated with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent from August 31, 2022, through September 26, 2022, VAERS received 779 reports (all U.S.) the majority (n=740, 95.0%) of which were non-serious reports. There were 15 reports among individuals aged 5-11 years (all non-serious with 14 of the 15 reports having no AEs reported). The top ten most frequently reported MedDRA preferred terms* (PTs) for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent include:

- Most frequent PTs (Bivalent Vaccine): headache, fatigue, pyrexia, pain, chills, nausea, dizziness, incorrect product formulation administered, pain in extremity, injection site pain.

As of September 13, 2022, there are 849,456 VAERS reports (411,880 U.S. reports) following vaccination with the original Pfizer-BioNTech COVID-19 Vaccine among all ages, including

71,827 reports (48,961 U.S.) following a 3rd, 4th, or 5th dose (i.e., booster dose) among individuals ≥12 years of age and 983 (978 U.S.) reports following a booster dose among individuals 5-11 years of age. The majority of U.S. VAERS reports for the original Pfizer-BioNTech COVID-19 Vaccine were non-serious (81.6% for any dose among all ages, 77.0% for booster doses among those aged ≥12 years, and 98.0% for booster doses among those aged 5-11 years). The top ten most frequently reported MedDRA preferred terms* (PTs) include (U.S. and foreign):

- Most frequent PTs among all ages and all doses (Original Vaccine): SARS-CoV-2 test, COVID-19, headache, fatigue, pyrexia, dizziness, pain, vaccination failure nausea, pain in extremity.
- Most frequent PTs among persons ≥12 years of age receiving a booster dose (Original Vaccine): SARS-CoV-2 test, immunization, COVID-19, headache, fatigue, pyrexia, off label use, interchange of vaccine products, pain, chills.
- Most frequent PTs among persons 5-11 years of age receiving a booster dose (Original Vaccine): product preparation issue, incorrect dose administered, expired product administered, product administered to patient of inappropriate age, product preparation error, extra dose administered, pyrexia, pain in extremity, product storage error, inappropriate schedule of product administration.
- Most frequent non-medication error-related PTs among persons 5-11 years receiving a booster dose (Original Vaccine): pyrexia, pain in extremity, fatigue, vomiting, dizziness, headache, injection site pain, nausea, pain, syncope.

*Note that a report may have one or more PTs.

Safety concerns previously identified from post-authorization safety surveillance data in VAERS for the original Pfizer-BioNTech COVID-19 Vaccine are summarized below. Anaphylaxis, myocarditis, and pericarditis are existing safety concerns that have been added to the product Fact Sheets.

Anaphylaxis

Post-authorization surveillance for the original Pfizer-BioNTech COVID-19 Vaccine identified a risk of anaphylaxis, occurring at a rate similar to reported rates of anaphylaxis following licensed preventive vaccines, primarily in individuals with history of prior severe allergic reactions to other medications or foods.[24,25] Anaphylaxis is an important identified risk in the PVP and included in the Warnings sections of the vaccine Fact Sheets and Prescribing Information. As of September 13, 2022, there have been 1,742 U.S. reports of anaphylaxis/anaphylactoid reaction following the original Pfizer-BioNTech COVID-19 Vaccine among individuals of all ages (based on an automated search). Among individuals vaccinated with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent from August 31, 2022, through September 26, 2022, there has been one VAERS report of anaphylaxis. PTs included in the automated VAERS query were as follows: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock. The estimated crude reporting rate for anaphylaxis following the original Pfizer-BioNTech COVID-19 Vaccine for all ages in the U.S. is 4.8 cases per million doses administered which is similar to estimated rates for other vaccines.[26]

Myocarditis and pericarditis

Post-EUA safety surveillance reports received by FDA and CDC identified increased rates of myocarditis and pericarditis, particularly 0-7-days following administration of the second primary series dose or first booster dose of the original Pfizer-BioNTech COVID-19 Vaccine. Reporting

rates for reports verified to meet the CDC case definition of myocarditis and pericarditis in VAERS have been generally higher among males under 40 years of age than among females and older males. The highest reporting rates have been in males 12 through 17 years of age (rates of verified cases per million doses 0-7-days following dose 2 administration of the original Pfizer-BioNTech COVID-19 Vaccine were 75.9 cases among males ages 16-17 years, 46.4 cases among males ages 12-15 years, and 2.6 cases among males ages 5-11 years). VAERS monitoring has also shown that reporting rates of myocarditis among individuals ages 12-29 years following a first booster dose of original Pfizer-BioNTech COVID-19 Vaccine exceeded background rates (rates of verified cases per million doses 0-7-days following first booster dose administration were 24.1 cases among males ages 16-17 years and 15.3 cases among males ages 12-15 years).[27]There were no verified reports of myocarditis/pericarditis following a first booster dose among individuals aged 5-11 years.[27]

Although some cases of vaccine-associated myocarditis/pericarditis following the original Pfizer-BioNTech COVID-19 Vaccine have required intensive care support, available data from short-term follow-up suggests that most individuals have had resolution of symptoms with conservative management. CDC is conducting enhanced surveillance for VAERS case reports using patient and healthcare provider surveys to assess functional status and clinical outcomes among individuals reported to have developed myocarditis after mRNA COVID-19 vaccination. Among individuals aged 12-29 years, available data from follow-up with cardiologists/healthcare providers at least 90 days after onset of myocarditis symptoms suggests most individuals fully recover from myocarditis following mRNA vaccination.[27] Information is not yet available about potential longer-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 PVP and included in the vaccine Fact Sheets and Prescribing Information (Section 5 Warnings and Precautions, 5.2 Myocarditis and Pericarditis, Section 6.2 Post Authorization Experience) for the original Pfizer-BioNTech COVID-19 Vaccine. The Sponsor is conducting additional post-authorization/post-marketing studies to assess known serious risks of myocarditis and pericarditis for the original and bivalent Pfizer-BioNTech COVID-19 Vaccine as well as to identify an unexpected serious risk of subclinical myocarditis for the original Pfizer-BioNTech COVID-19 Vaccine. To help ensure appropriate monitoring of such risks and protect public health, the Sponsor and vaccination providers will be required, under the conditions of authorization, to report all cases of myocarditis and pericarditis (regardless of seriousness) to VAERS. Because some cases of myocarditis or pericarditis following vaccine administration are conservatively managed and may not meet the definition of serious adverse events, this will help ensure that all cases are reported by the Sponsor and vaccination providers.

Review of the above VAERS data, as well as ongoing review of VAERS data and the Sponsor's periodic safety reports, did not identify new safety concerns for the original or bivalent Pfizer-BioNTech COVID-19 Vaccine. Most AEs are labeled events, including anaphylaxis and myocarditis/pericarditis, and consistent with the known safety profile for the original vaccine. No unusual frequency, clusters, or other trends for AEs were identified that would suggest new safety concerns for the original or bivalent vaccine.

7 FDA Review of Other Information Submitted in support of the EUA Amendment

7.1 Chemistry, Manufacturing, and Control (CMC) Information

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) contains two mRNA constructs, one encoding the spike protein from the original SARS-CoV-2 strain (Original; Wuhan-Hu-1) and the other encoding the spike protein from the SARS-CoV-2 Omicron BA.4/BA.5 variant. The bivalent vaccine is formulated in Tris/Sucrose buffer as a 10-µg mRNA dose (5 µg of each mRNA construct). Each bivalent dose also contains the following ingredients: a total lipid content of 0.25 mg (ALC-0315, ALC-0159, DSPC, and cholesterol), 0.02 mg tromethamine (Tris base), 0.13 mg tromethamine hydrochloride (Tris-HCl), 10.3 mg sucrose and 0.9 mg sodium chloride (from diluent).

The 10-µg mRNA dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is supplied as a multi-dose vial filled at 1.3 mL fill volume and requires dilution with 1.3 mL 0.9% sodium chloride prior to administration. Each vial provides 10 doses of vaccine post-dilution with each dose in a 0.2 mL injection volume. The shelf life of the bivalent vaccine is set to be 12 months when stored frozen at -90°C to -60°C in vials. The established shelf life also includes an allowance for short-term storage at 2°C to 8°C for up to 10 weeks at the point of use, counted within the 12-month shelf life.

The manufacturing process for the 10-µg mRNA dose of the bivalent vaccine is essentially the same as that used for the previously authorized 30-µg mRNA dose with the exception of the final fill volumes: 2.25 mL and 1.3 mL for the 30- and 10-µg doses supplied in multi-dose vials, respectively. Consistent manufacturing of the Pfizer-BioNTech COVID-19 vaccine at the fill volume of 1.3 mL for the 10-µg mRNA dose has previously been demonstrated based on process validation data from the monovalent (Original) vaccine. A commercial-scale emergency-supply of bivalent (Original and Omicron BA.4/BA.5) vaccine at the 10-µg mRNA dose was manufactured at an existing facility previously included in the EUA for the original Pfizer-BioNTech COVID-19 Vaccine. This confirmatory lot met all release specifications, supporting the manufacturing and filling process for the bivalent vaccine product at a dosage level of 10-µg mRNA with acceptable quality.

The specifications for the 10-µg mRNA dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) remain the same as those used for the 30-µg mRNA dose with one modification to the “Vial Content (volume)” to account for the fill volume change. The analytical procedures for the bivalent vaccine release and stability testing remain unchanged.

The manufacture of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is performed at existing facilities that were previously included in the EUA for the manufacture of the Original Pfizer-BioNTech COVID-19 Vaccine. These facilities are currently included in the EUA for the manufacture of the authorized 30 ug/dose bivalent vaccine. No changes were made to the facilities’ equipment, container closure systems, quality systems and controls. We find that all facilities within the scope of this authorization are adequate to support the use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5 presentation for individuals 5 through 11 years of age under an Emergency Use Authorization.

7.2 Pharmacovigilance Activities

Pfizer is conducting safety-related post-authorization/post-marketing studies for the monovalent vaccine, including post-marketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. Pfizer submitted a revised pharmacovigilance plan to monitor safety concerns that could be associated with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). The plan includes the following safety concerns:

- Important Identified Risks: anaphylaxis, myocarditis, and pericarditis
- Important Potential Risks: Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.

Sponsor pharmacovigilance activities

The Sponsor will conduct passive and active surveillance to monitor the post-authorization safety for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), including:

- Mandatory reporting by the Sponsor under the EUA for the following events to VAERS within 15 days: SAEs (irrespective of attribution to vaccination); myocarditis; pericarditis; multisystem inflammatory syndrome (MIS) in children and adults; COVID-19 resulting in hospitalization or death
- Periodic safety reports containing an aggregate review of safety data including assessment of AEs; vaccine administration errors, whether or not associated with an AE; and newly identified safety concerns.
- Post-authorization observational studies to evaluate the association between Pfizer-BioNTech COVID-19 Vaccine, Bivalent and a pre-specified list of adverse events of special interest (AESIs), including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The studies should be conducted in large scale databases with an active comparator. This condition of authorization under the EUA, to conduct post-authorization observational studies, will encompass the evaluation of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals <12 years of age in the following studies:

    - C4591021: Post-Authorization/Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine.

      Objective: To assess the potential increased risk of prespecified AESIs, including myocarditis/pericarditis, after being vaccinated with COVID-19 vaccine, including the Bivalent Omicron modified vaccine, if feasible.

    - C4591036: Pediatric Heart Network (PHN) Study: Low interventional cohort study of myocarditis/pericarditis associated with Comirnaty in persons less than 21 years of age

      Objective: To characterize the clinical course, risk factors, resolution, long-term sequelae, and quality of life in children and young adults <21 years with acute post-vaccine myocarditis/pericarditis, including myocarditis/pericarditis after the Bivalent Omicron-modified vaccine, if feasible.

- C4591012: Post-emergency use authorization active safety surveillance study among individuals in the Veteran's Affairs Health System receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) vaccine.

  Objective: To assess whether individuals in the U.S. Veteran's Affairs Health System experience increased risk of safety events of interest, including myocarditis and pericarditis, following receipt of the Pfizer-BioNTech COVID-19 Vaccine, including the Bivalent Omicron modified vaccine, if feasible.

In addition, the Sponsor will conduct a new stand-alone post-authorization observational study to evaluate the association between the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and a pre-specified list of AESIs in the general U.S. population who will receive a bivalent booster dose in the U.S. The Sponsor also plans to include vaccine effectiveness analyses among individuals in all authorized age groups who receive the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in Study C4591014 entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study Kaiser Permanente Southern California".

Other pharmacovigilance activities

Mandatory reporting by vaccination providers to VAERS, and to the extent feasible, to the Sponsor, for the following events:

- Vaccine administration errors whether or not associated with an AE
- Serious AEs (irrespective of attribution to vaccination)
- Myocarditis
- Pericarditis
- Cases of multisystem inflammatory syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

Active surveillance of vaccine recipients via the v-safe program: v-safe is a smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine parents/guardians (or the recipient) for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports medically significant AE.

7.3 EUA Prescribing Information and Fact Sheets

The Full EUA Prescribing Information, Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers), and Vaccine Information Fact Sheet for Recipients and Caregivers were reviewed, and suggested revisions were sent to the Sponsor. The revised Fact Sheets are accurate, not misleading, and appropriate for the proposed use of the product under EUA.

8 Benefit/Risk in the Context of the Proposed EUA For Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) Booster Dose in Individuals 5-11 Years of Age

8.1 Discussion of Benefits, Risks, and Uncertainties

COVID-19 is caused by SARS-CoV-2 and the virus has been responsible for over 96 million cases of COVID-19 and over 1 million deaths in the US. Since the start of the pandemic, there

has been a succession of COVID-19 variants including Beta, Delta, Omicron BA.1 and most recently Omicron BA.5. Current treatment options for COVID-19 in individuals 5-11 years of age include antiviral medications, convalescent plasma, and immune modulators approved or authorized for the management of individuals with COVID-19. Although treatments exist for those infected with SARS-CoV-2 they are usually not effective in severe disease. Additionally, such treatments may not prevent complications from COVID-19 including post-acute sequelae of COVID-19 (long COVID).

In addition to the currently authorized and approved treatments, FDA approved and authorized vaccines provide protection to individuals against COVID-19 and play an important role in controlling the pandemic and reducing the societal and economic interruption caused by the pandemic. There are currently 2 authorized COVID-19 vaccines for disease prevention in individuals 5-11 years of age, which are the two mRNA-based vaccines from Moderna and Pfizer- BioNTech. These monovalent vaccines are based on the original (ancestral) strain of SARS-CoV-2 and some vaccines initially had effectiveness of up to 90 to 95% against symptomatic disease. A succession of viral variants and waning of individual immunity has led to a reduction in vaccine effectiveness over time. In the setting of the viral variants that have emerged, boosting with available vaccines (based on the ancestral strain) has been able to restore some degree of protection against serious and symptomatic disease, but it appears that effectiveness against transmission and symptomatic disease declines more rapidly than that against serious disease, as has been illustrated by studies conducted in the United States,[28,29] Israel,[17] Qatar,[14] Portugal,[30] and England.[9]

The immunogenicity and safety of mRNA booster vaccines developed against the Beta, Delta, and Omicron BA.1 variants have previously been evaluated by both Moderna and Pfizer-BioNTech. However, these booster vaccines were not deployed in the United States due to the rapid evolution of the SARS-CoV-2 variants. In addition to those clinical data, nonclinical studies indicate that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose will provoke an antibody response to current predominantly circulating BA.4 and BA.5 variants which is several-fold higher than the response provoked by the original (monovalent) vaccine.

Based on previous experience and available evidence, vaccination with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) booster dose is expected to provoke a stronger immune response to the currently circulating BA.4 and BA.5 variants. That noted, it is uncertain exactly how the magnitude of the increase in antibody response to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) booster dose will translate into effectiveness against specific COVID-19 outcomes in humans, including symptomatic and serious disease with currently circulating variants, and this uncertainty is even greater for potential variants that may emerge in the future.

Additional booster doses may be associated with transient local and systemic symptoms like those seen with primary series and booster doses given previously. The most notable uncommon side effect of the mRNA COVID-19 vaccines has been myocarditis. Based on the data from the BEST Initiative, within a week after the second dose of Pfizer COVID-19 vaccine primary series, the crude observed ratio (with adjustment for claims processing delay) of myocarditis or pericarditis was 0.73 cases per 100,000 vaccine doses among individuals aged 5-11 years, and 0.95 cases per 100,000 vaccine doses among male individuals aged 5-11 years (unpublished data, based on fewer than 10 cases). The Moderna vaccine was authorized in June 2022 for this age group so there is not sufficient data accumulated for the Moderna COVID-19 vaccine in this age group, and an equivalent measure for the Moderna COVID-19 vaccine cannot be estimated at this time. The myocarditis associated with the administration of

mRNA COVID-19 vaccines has been mild and transient in most cases (>95%). Limited clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested any new safety concerns in addition to those previously characterized. In addition, passive and active surveillance systems will be utilized to continuously monitor adverse reactions and any emerging safety concerns post EUA.

The totality of the available evidence indicates that Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster doses will likely increase the immune response against SARS-CoV-2 variants and may particularly help target the currently predominant BA.5 variant. Administration of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster is appropriate for all individuals 5-11 years of age at least two months after previous primary or booster vaccination but is particularly important in those individuals who have never been previously boosted since protection against symptomatic and serious COVID-19 may have waned over time since administration of the primary series.

Limited clinical evaluation of bivalent mRNA COVID-19 vaccine formulations has not suggested any new safety concerns additional to the extensively characterized safety profile of originally authorized and approved mRNA COVID-19 vaccines, and post-deployment monitoring for adverse events using both passive and active surveillance systems will be utilized to assess whether any new safety concerns emerge. Table 1 provides a summary of the benefit risk considerations in a standard FDA format.

Table 1. Summary of Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19 caused by SARS-CoV-2 has been responsible for over 96 million cases and over 1 million deaths in the US • There has been a succession of variants (Delta, Omicron BA.1 and most recently BA.5) that have led to a reduction in vaccine effectiveness • Although the available COVID-19 vaccines based on the original (ancestral) strain continue to provide some protection against hospitalization and death, their overall effectiveness appears to have decreased	• COVID-19 is a serious disease associated with significant morbidity and mortality from initial infection and additional morbidity from post-acute sequelae of COVID-19 (long COVID) in a subset of those individuals • Certain available COVID-19 vaccines initially had high effectiveness (90-95%) against symptomatic disease; however, vaccine effectiveness has declined in the setting of the recent Omicron variant in combination with waning individual immunity; this effect is most clearly observed in older individuals, but decreased vaccine effectiveness, especially after the primary series, is also apparent in pediatric age groups.
Current Treatment Options	• An antiviral medication, immune modulators, and convalescent plasma, have been approved or authorized for the management of individuals with COVID-19 There are two authorized mRNA COVID-19 vaccines for use as a primary series in individuals 5-11 years of age; the vaccine from Pfizer-BioNTech is authorized for use as a booster dose	• Although treatments exist for those infected with SARS-CoV-2, they are usually not effective in severe disease; additionally, treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID) • Vaccines play an important role in pandemic control and provide important protection.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The immunogenicity and safety of booster vaccines against Beta, Delta, and Omicron BA.1 variants were previously evaluated by both current mRNA vaccine manufacturers; however, these vaccines were not deployed in the US because of SARS- CoV-2 variant evolution • Non-clinical studies indicate that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose will provoke an antibody response against BA.4 and BA.5 that is many-fold higher than the Original booster • Uncertain how the magnitude of the increase in antibody response in humans will translate into effectiveness against COVID-19 outcomes, including symptomatic and serious disease	• The totality of the available evidence indicates that bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster doses will likely increase the broad immune response against SARS-CoV-2 variants and may particularly help target the currently predominant BA.5 variant • Administration of bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster doses is appropriate for all previously vaccinated individuals 5-11 years of age regardless of the number of prior COVID-19 vaccinations, but especially those who have never been previously boosted since protection against serious disease may have waned over time since administration of the primary series

8.2 Conclusions Regarding Benefit-Risk

For individuals 5-11 years of age, the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine booster dose outweigh the known and potential risks of the bivalent booster considering the totality of available evidence and the outstanding uncertainties. The benefit-risk profile of available mRNA COVID-19 vaccines is well understood following the administration of over one billion doses. FDA's previous benefit-risk assessments based on real-world evidence clearly demonstrated that the benefits of available COVID-19 vaccines outweigh their risks. During the current wave of COVID-19 caused in large part by the BA.5 sublineage, administration of a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose is expected to have a favorable benefit-risk profile, potentially not only restoring protection against serious outcomes from COVID-19, but also by reducing symptomatic disease that may be followed by debilitating post-acute COVID-19 syndrome. Broader protection against COVID-19 variants potentially elicited by the bivalent vaccine may also help protect against future emerging variants.

9 Overall Summary and Recommendations

Following review of information submitted in support of the EUA request, and VRBPAC recommendations from the June 28, 2022, meeting, the review team considered the following in its assessment of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5):

- As summarized in Section 2 of this review, the 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.

- The scientific evidence available to support this EUA request was as follows:
  - clinical safety and immunogenicity data from a study which evaluated a second booster dose with the Bivalent BA.1(Original and Omicron BA.1) vaccine following a primary series and first booster with the original Pfizer-BioNTech COVID-19 Vaccine,

- clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated primary and booster vaccination with the original Pfizer-BioNTech COVID-19 Vaccine,
- post-marketing safety surveillance data with primary series and booster doses of the original Pfizer-BioNTech COVID-19 Vaccine, and
- non-clinical immunogenicity data from a study of BNT162b2 formulations containing an Omicron BA.4/BA.5 component.

- Based on the totality of available scientific evidence, it is reasonable to conclude that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), when administered as a single booster dose to individuals 5-11 years of age who have completed primary vaccination or a booster dose of an authorized or approved COVID-19 vaccine at least 2 months prior, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages BA.4/BA.5. As summarized in Section 5, vaccine effectiveness was inferred based on extrapolation of clinical immunogenicity data from evaluation of a related bivalent COVID-19 vaccine (manufactured using the same process as the original Pfizer-BioNTech COVID-19 vaccine and containing original and Omicron BA.1 components) in adults >55 years of age. These data demonstrated statistically superior neutralizing antibody responses against Omicron BA.1, and statistically non-inferior neutralizing antibody responses against the original strain, for the bivalent vaccine compared to the original vaccine.

- Based on FDA's review of the available scientific evidence, including the data summarized in Section 6 and assessment of benefits and risks in Section 8 of this review, the known and potential benefits of a booster dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) outweigh the known and potential risks when used as a booster dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 5-11 years of age. Known and potential benefits include reduction in the risk of symptomatic COVID-19 and associated serious sequelae, including from COVID-19 due to Omicron variant sublineages BA.4 and BA.5. Uncertainties related to benefits include that effectiveness of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to prevent COVID-19 is inferred and extrapolated from immunogenicity data with a different Omicron-containing bivalent vaccine (Original and Omicron BA.1) manufactured by the same process. It is also uncertain how any given magnitude of the increase in antibody response to a bivalent (Original and BA.4/BA.5) booster vaccine, relative to the original (monovalent) vaccine, will translate into effectiveness against COVID-19 outcomes, including symptomatic disease. However, this uncertainty is considered against available evidence demonstrating waning protection from COVID-19 vaccine primary series and booster doses, decreased effectiveness of currently available COVID-19 vaccines against Omicron BA.5 (the predominant SARS-CoV-2 sublineage in the US) compared to previous strains, and the time that would be needed to accrue clinical trial data with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to more directly assess effectiveness. Additional uncertainties include effectiveness against future SARS-CoV-2 variants, effectiveness against asymptomatic SARS-CoV-2 infection and SARS-CoV-2 transmission, and effectiveness in certain high-risk populations such as severely immunocompromised individuals. Known and potential risks include generally self-limited common local and systemic adverse reactions (notably injection site reactions, fatigue, headache, muscle pain, chills, fever and joint pain), lymphadenopathy, and rarely anaphylaxis and myocarditis/pericarditis based on experience in original Pfizer-BioNTech COVID-19 Vaccine recipients 5-11 years of age. Risks that should be further evaluated include quantifying the rate of vaccine-associated myocarditis/pericarditis in this age group

and surveillance for other adverse reactions that may become apparent with widespread use of the vaccine and with longer duration of follow-up.

- The Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is currently authorized under EUA for use as a single booster dose administered at least 2 months after either completion of primary vaccination or the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine in individuals 12 years of age and older. The original (monovalent) Pfizer-BioNTech COVID-19 Vaccine, based on the ancestral SARS-CoV-2 strain, is currently authorized for use under EUA as a first booster dose in individuals 5-11 years of age. COVID-19 vaccines based on currently circulating variants of concern are not currently approved or available for use in individuals 5-11 years of age.

Based on the considerations outlined above, the review team recommends authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) under EUA for use as a single booster dose administered at least 2 months after either completion of primary vaccination or the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine in individuals 5-11 years of age. The review team also recommends a revision to the existing EUA for Pfizer-BioNTech COVID-19 Vaccine to remove the use of the monovalent vaccine as a booster dose for individuals 5-11 years of age because the benefit/risk profile for this currently-authorized booster dose use is expected to be inferior against the currently circulating Omicron variant compared to Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

10 References

[1] Johns Hopkins Coronavirus Resource Center (website) https://coronavirus.jhu.edu/ Accessed October 4, 2022

[2] Centers for Disease Control and Prevention, 2022. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. (website) https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html Accessed August 26, 2022.

[3] Centers for Disease Control and Prevention, 2021. Post-COVID Conditions: Overview for Healthcare Providers. (website) https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html Accessed August 26, 2022.

[4] Irfan O, Muttalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis [published online ahead of print, 2021 Feb 16]. *Arch Dis Child*. 2021;106(5):440-448.

[5] Liguoro I, Pilotto C, Bonanni M, et al. SARS-COV-2 infection in children and newborns: a systematic review [published correction appears in Eur J Pediatr. 2021 Jul;180(7):2343]. *Eur J Pediatr*. 2020;179(7):1029-1046.

[6] Assaker R, Colas AE, Julien-Marsollier F, et al. Presenting symptoms of COVID-19 in children: a meta-analysis of published studies. *Br J Anaesth*. 2020;125(3):e330-e332.

[7] Poline J, Gaschignard J, Leblanc C, et al. Systematic Severe Acute Respiratory Syndrome Coronavirus 2 Screening at Hospital Admission in Children: A French Prospective Multicenter Study. *Clin Infect Dis.* 2021;72(12):2215-2217.

[8] Centers for Disease Control and Prevention, 2021. COVID Data Tracker (website) https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases Accessed October 4, 2022.

[9] Centers for Disease Control and Prevention, 2021. COVID Data Tracker (website) https://covid.cdc.gov/covid-data-tracker/#demographics Accessed October 4, 2022.

[10] Centers for Disease Control and Prevention, 2021. COVID Data Tracker (website) https://covid.cdc.gov/covid-data-tracker/#nowcast-heading Accessed October 4, 2022.

[11] Pulliam JRC, van Schalkwyk C, Govender N, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. *Science*. 2022;376(6593):eabn4947.

[12] Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants [published correction appears in Nat Med. 2022 Apr 21;:]. *Nat Med*. 2022;28(5):1063-1071. doi:10.1038/s41591-022-01753-y.

[13] Andrews N, Stowe J, Kirsebom F, et al. Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. *N Engl J Med*. 2022;386(16):1532-1546.

[14] Taylor CA, Whitaker M, Anglin O, et al. COVID-19–Associated Hospitalizations Among Adults During SARS-CoV-2 Delta and Omicron Variant Predominance, by Race/Ethnicity and Vaccination Status — COVID-NET, 14 States, July 2021–January 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:466–473. DOI: https://www.cdc.gov/mmwr/volumes/71/wr/mm7112e2.htm.

[15] Korves C, Izurieta HS, Smith J, et al. Relative effectiveness of booster vs. 2-dose mRNA Covid-19 vaccination in the Veterans Health Administration: Self-controlled risk interval analysis. *Vaccine*. 2022;40(33):4742-4747.

[16] Stowe J, Andrews N, Kirsebom F, Ramsay M, Bernal JL. Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation: test negative case-control study. medRxiv. 2022 Jan 1.

[17] Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-Dose and 3-Dose Effectiveness 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 Morb Mortal Wkly Rep* 2022;71:255–263. DOI: https://www.cdc.gov/mmwr/volumes/71/wr/mm7107e2.htm

[18] Chemaitelly H, Ayoub HH, AlMukdad S, et al. Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar. *Nat Commun*. 2022;13(1):3082. Published 2022 Jun 2.

[19] Tenforde MW, Patel MM, Gaglani M, et al. Effectiveness of a Third Dose of Pfizer-BioNTech and Moderna Vaccines in Preventing COVID-19 Hospitalization Among Immunocompetent and Immunocompromised Adults — United States, August–December 2021. *MMWR Morb Mortal Wkly Rep* 2022; 71:118–124. https://www.cdc.gov/mmwr/volumes/71/wr/mm7104a2.htm

[20] Arbel R, Sergienko R, Friger M, et al: BNT162b2 vaccine booster and mortality due to COVID 19. *N Engl J Med* 2021; 385:2413-2420.

[21] Bar-On YM, Goldberg Y, Mandel M, et al. Protection by a Fourth Dose of BNT162b2 against Omicron in Israel. *N Engl J Med*. 2022;386(18):1712-1720. doi:10.1056/NEJMoa2201570

[22] Gazit S, Saciuk Y, Perez G, et al. Relative Effectiveness of Four Doses Compared to Three Dose of the BNT162b2 Vaccine in Israel. *medRxiv* 2022.03.24.22272835; https://doi.org/10.1101/2022.03.24.22272835. Preprint.

[23] Atmar RL, Lyke KE, Deming ME et al. Homologous and Heterologous Covid-19 Booster Vaccinations. N Engl J Med 2022; 386:1046-105.

[24] Gee J, Marquez P, Su J, et al. First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:283–288. http://dx.doi.org/10.15585/mmwr.mm7008e3

[25] Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020. *MMWR Morb Mortal Wkly Rep* 2021;70:46–51. http://dx.doi.org/10.15585/mmwr.mm7002e1

[26] McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol.* 2016;137(3):868-878.

[27] Shimabukuro, T. Updates on vaccine-associated myocarditis; presented to the Advisory Committee on Immunization Practices on July 19, 2022. Available at: ACIP July 19, 2022 Presentation Slides | Immunization Practices | CDC; Accessed on August 23, 2022.

[28] Lauring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, McNeal T, Ghamande S, Douin DJ, Talbot HK, Casey JD, Mohr NM. Clinical severity and mRNA vaccine effectiveness for omicron, delta, and alpha SARS-CoV-2 variants in the United States: a prospective observational study. MedRxiv. 2022 Feb 7.

[29] Dorabawila V, Hoefer D, Bauer UE, Bassett M, Lutterloh E, Rosenberg E. Effectiveness of the BNT162b2 vaccine among children 5-11 and 12-17 years in New York after the Emergence of the Omicron Variant. medRxiv. 2022 Jan 1.

[30] Kislaya I, Casaca P, Borges V, Sousa C, Ferreira B, Fernandes E, Dias CM, Duarte S, Almeida JP, Coelho L, Grenho I. SARS-CoV-2 BA. 5 vaccine breakthrough risk and severity compared with BA. 2: a case-case and cohort study using Electronic Health Records in Portugal. medRxiv. 2022 Jan 1.