

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

Identifying Information

Application Type	EUA Amendment
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Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech
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Review Completion Date	December 8, 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	<p>Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)</p> <p>Use: As the third dose of the Pfizer-BioNTech primary vaccination series following two doses of the Pfizer-BioNTech COVID-19 Vaccine in individuals 6 months through 4 years of age</p>
Intended Population	Individuals 6 months through 4 years of age

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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 December 2, 2022, has led to over 640 million cases of coronavirus disease 2019 (COVID-19), including over 6.6 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 (recently including 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 the World Health Organization (WHO) and 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. On October 12, 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 5 through 11 years of age 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.

Evidence considered by FDA to support the October 12, 2022, authorization of the Pfizer BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 5 through 11 years of age included:

- 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 U.S. because of SARS-CoV-2 variant evolution
- Non-clinical studies indicated that a bivalent (Original and BA.4/BA.5) mRNA COVID-19 vaccine booster dose will elicit an antibody response against BA.4 and BA.5 that is many-fold higher than the Original booster

The totality of the evidence led to the conclusion that while clinical data for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) were not yet available, the

bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster doses would likely increase the broad immune response against SARS-CoV-2 variants, including when given as a single booster dose to individuals 5 through 11 years of age.

The Pfizer BioNTech COVID-19 Vaccine was first authorized on June 17, 2022, as a three dose primary series for children 6 months through 4 years of age. In the current EUA request submission, Pfizer requested that the third dose of the Pfizer-BioNTech COVID-19 primary series for individuals 6 months through 4 years of age be changed from the Pfizer-BioNTech COVID-19 Vaccine to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to better match the currently circulating SARS-CoV-2 variants. A change in the third dose only was requested to align with the current situation in older individuals who are receiving a two dose primary series of the Pfizer-BioNTech COVID-19 Vaccine to provide a base level of protection against a broad array of SARS-CoV-2 variants, followed by a booster of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to improve protection against the currently circulating Omicron variants. Further rationale provided is: 1) recent immunogenicity data obtained with currently circulating variants demonstrate better neutralization with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), 2) extrapolation of immunogenicity and safety for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to the 6 month through 4-year age group is reasonable based upon prior experience with other vaccines, including the Pfizer-BioNTech COVID-19 Vaccine, and 3) no new safety concerns have been identified in individuals 5 years of age and older receiving the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Pfizer has also provided the manufacturing and product-quality information needed to support authorization of the presentation intended for use in individuals 6 months through 4 years of age. No concerns were identified upon review of the manufacturing information submitted.

The approach proposed by Pfizer is additionally supported by data from a recently published observational study of the effectiveness of bivalent mRNA booster vaccines in preventing symptomatic SARS-CoV-2 infection during circulation of BA.4/BA.5 and their sublineages, which demonstrated that bivalent booster doses provided additional protection against symptomatic SARS-CoV-2 infection and were relatively 28 to 56% more effective than the monovalent mRNA COVID-19 vaccines.² Review of the available clinical evidence in adults also indicates that the bivalent mRNA COVID-19 vaccines produce immune responses against the currently circulating BQ.1, BQ1.1, and XBB Omicron variants that are several-fold higher than those produced by the original monovalent mRNA COVID-19 vaccines.

Post-marketing safety data for the Pfizer-BioNTech COVID-19 Vaccine are also 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 November 27, 2022, more than 388 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 (Original and Omicron BA.4/BA.5) were headache, fatigue, COVID-19, pyrexia, pain, chills, nausea, dizziness, pain in extremity, and cough. 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 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 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 U.S. population.

The totality of scientific evidence available at this time supports the conclusion that revising the third dose of the COVID-19 primary vaccination series for individuals 6 months through 4 years of age from the Pfizer-BioNTech COVID-19 Vaccine to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to better match the currently circulating SARS-CoV-2 variants 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 as the third dose of the COVID-19 primary vaccination series for individual 6 months through 4 years of age. The review team also recommends that the authorization no longer provide for the use of the Pfizer-BioNTech COVID-19 Vaccine as a third dose in the primary series in this age group, as circumstances exist that make it appropriate to make this revision to protect the public health. The revised Pfizer-BioNTech primary vaccination series for individuals 6 months through 4 years of age will therefore consist of the first two doses of Pfizer-BioNTech COVID-19 Vaccine given at least 3 weeks apart followed by a third dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) at least 8 weeks later.

2 Background

2.1 SARS-CoV-2 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,³ 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.⁴ 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.^{5,6} 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.^{7,8} 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 December 2, 2022, has led to over 640 million cases of COVID-19 and over 6.6 million deaths worldwide.¹ In the U.S., more than 98 million cases and 1 million deaths have been reported to

the Centers for Disease Control and Prevention (CDC).⁹ Over 2% of cases occurred in children 6 months through 4 years of age.¹⁰

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 U.S., have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently Omicron BA.5, BQ.1, and BQ.1.1. The Omicron variant BA.1 became the predominant variant circulating in the U.S. in December 2021, and while COVID-19 cases, hospitalizations, and deaths in the U.S. have declined since the peak of the Omicron surge in January 2022, the Omicron variant continues to evolve into sublineages, including BA.4 and BA.5 sublineages, and more recently the BQ.1 and BQ.1.1 sublineages that have been associated with recent increases in COVID-19 case rates.¹¹ Both the BQ.1.1 sublineages are notable because they are not neutralized by the monoclonal antibody preparations currently available in the United States.¹² Population-level evidence suggests an increased reinfection risk associated with sublineages of the Omicron variant compared to earlier SARS-CoV-2 variants.¹³ Additionally, available evidence demonstrates waning of immunity elicited by COVID-19 primary vaccination and monovalent booster doses. This corresponds with reduced effectiveness of the currently available vaccines based on the original SARS-CoV-2 strain against COVID-19 caused by the currently dominant Omicron sublineages (see Section 3.1 below). Consequently, a vaccine able to elicit improved protection against the evolving Omicron sublineages is an important public health need.

Throughout this document, the term “sublineage” indicates the SARS-CoV-2 Omicron variant BA.1, BA.4, BA.5, BQ.1, BQ.1.1 and/or XBB 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 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 5 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 6 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. Novavax COVID-19 Vaccine, Adjuvanted is also authorized for use as a first booster dose administered at least 6 months after completion of primary vaccination with an authorized or approved COVID-19 Vaccine in individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine. The authorized dosing interval for a booster is at least 6 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine. 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.

Monoclonal antibodies have been previously deployed for prophylaxis and for treatment of COVID-19 in older children and adults. However, some variants have emerged that are relatively resistant to neutralization by the existing monoclonal antibodies. FDA recently announced that bebtelovimab is not currently authorized in the United States because it is not expected to neutralize Omicron variants BQ.1 and BQ1.1.

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 monovalent COVID-19 vaccines in the U.S. 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 monovalent 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.^{14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24}

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.^{14, 15, 16} Although first booster doses with the monovalent original COVID-19 vaccines have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron,^{14, 15, 16, 17} 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^{14, 18, 29, 20} and lower effectiveness among the immunocompromised individuals.²¹ In Israeli experience with a second booster dose of the Original 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.^{23, 24}

In a recently published observational study of the effectiveness of bivalent mRNA booster vaccines in preventing symptomatic SARS-CoV-2 infection during circulation of BA.4/BA.5 and their sublineages, the relative vaccine effectiveness (rVE) of a bivalent booster dose compared with that of ≥ 2 monovalent vaccine doses among persons for whom 2–3 months and ≥ 8 months had elapsed since last monovalent dose was 30% and 56% among persons 18–49 years of age, 31% and 48% among persons 50–64 years of age, and 28% and 43% among persons ≥ 65 years of age, respectively. Absolute vaccine effectiveness after ≥ 2 monovalent vaccine doses against symptomatic SARS-CoV-2 infection was 43% (95% CI: 39–46%) among persons aged 18–49 years, 28% (95% CI: 22–33%) among persons 50–64 years of age, and 22% (95% CI: 15–29%) among persons ≥ 65 years of age.²

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, 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 U.S. 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 [ICMRA 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 EUA 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.

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 to Replace the Third Primary Series Dose of the Pfizer-BioNTech COVID-19 Vaccine Given to Individuals 6 Months Through 4 Years of Age with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)

5.1 Summary of the EUA Request

On December 2, 2022, Pfizer and BioNTech submitted a request to amend the EUA to include the use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 6 months through 4 years of age as the third dose of the primary series, administered at least 8 weeks following the second dose of the primary series. This will replace Pfizer-BioNTech COVID-19 Vaccine as the third dose in the primary series. Each 3- μ g dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is formulated to contain 1.5 μ g of a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of the original SARS-CoV-2 strain and 1.5 μ g of modRNA encoding the S glycoprotein of SARS-CoV-2 Omicron sublineages 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.

A change in the third dose only was requested by Pfizer to align with the current situation in older individuals who are receiving a two dose primary series of the Pfizer-BioNTech COVID-19 Vaccine to provide a base level of protection against a broad array of SARS-CoV-2 variants, followed by a booster of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to improve protection against the currently circulating Omicron variants. Further rationale provided is: 1) recent immunogenicity data obtained with currently circulating variants demonstrate better neutralization with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), 2) extrapolation of immunogenicity and safety for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to the 6 month through 4-year age group is reasonable based upon prior experience with other vaccines, including the Pfizer-BioNTech COVID-19 Vaccine, and 3) no new safety concerns have been identified in individuals 5 years of age and older receiving the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Pfizer has also provided the manufacturing and product-quality information needed to support authorization of the presentation intended for use in individuals 6 months through 4 years of age. No concerns were identified upon review of the manufacturing information submitted.

5.2 Initial Clinical Effectiveness Data in Adults Using the Bivalent mRNA Boosters

CDC recently reported initial effectiveness results using the Bivalent mRNA (Original + Omicron BA.4/BA.5) boosters.² The study evaluated symptomatic cases of COVID-19 that were diagnosed from September 14, 2022, to November 11, 2022, in 360,626 adults who presented to the Increasing Community Access to Testing Program for COVID-19 testing. Of those tested, 34% of individuals were diagnosed with COVID-19. Relative vaccine effectiveness of a Bivalent mRNA booster dose compared with that of ≥ 2 monovalent mRNA vaccine doses among persons for whom 2 to 3 months and ≥ 8 months had elapsed since last monovalent mRNA dose was 30% and 56% among persons 18 to 49 year of age, 31% and 48% among persons 50 to 64 years of age, and 28% and 43% among persons ≥ 65 years of age, respectively. The authors concluded that Bivalent mRNA booster doses provide additional protection against symptomatic SARS-CoV-2 in immunocompetent persons who previously received monovalent mRNA vaccines only, with relative benefits increasing with time since receipt of the most recent

monovalent mRNA vaccine dose.

5.3 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 that build on the base of protection afforded by the authorized monovalent vaccines and 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 5 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 and the October 12, 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) as a booster dose in individuals 5 years of age and older was based on extrapolation of available immunogenicity and safety data from a clinical trial that evaluated the Pfizer-BioNTech 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 BA.4/BA.5) as a booster dose in individuals 5 years of age and older 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 Pfizer-BioNTech 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.²⁵

As mentioned in Section 4.2 above, FDA considers that safety and effectiveness data for a Bivalent mRNA COVID-19 vaccine accrued in a certain age group could be extrapolated to support EUA 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) EUA of a booster dose of any COVID-19 vaccine manufactured by the same process as the bivalent vaccine. Accordingly, FDA extrapolated from safety and effectiveness data for older age groups to support the use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as a booster dose in individuals 5 years of age and older.

For the Pfizer-BioNTech COVID-19 Vaccine, the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) has now been authorized under EUA for use as a booster dose in individuals 5 years of age and older as noted in the [October 12, 2022 FDA Decision Memorandum](#).

In the specific case of this EUA request from Pfizer, FDA is not considering extrapolation to support a booster dose use. However, FDA considers that the third dose of the primary vaccination series in individuals 6 months through 4 years of age is reasonably analogous to a

first booster dose in older individuals, because a third primary series dose builds on the protection provided by prior administration of the monovalent vaccine in a manner that is similar to a booster dose. In addition, given the notably reduced effectiveness of the original monovalent mRNA COVID-19 vaccines against currently circulating Omicron variants, FDA has determined that it is reasonable to replace the third original monovalent dose of the primary series in individuals 6 months through 4 years of age with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).¹¹ 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 6 months through 4 years of age was previously not available but is now included in the current EUA request submission.

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 6 months of age and older, and that it is also reasonable to extrapolate this data for use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine as the third dose in a three-dose primary series. This change in the third dose generally aligns with the current situation in older individuals who are receiving a two dose primary series of the Pfizer-BioNTech COVID-19 Vaccine to provide a base level of protection against a broad array of SARS-CoV-2 variants, followed by a booster of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) to improve protection against the currently circulating Omicron variants.

5.4 Basis for EUA Revision to Remove Authorization of the Original Pfizer-BioNTech COVID-19 Vaccine as a Third Primary Series 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 above, the monovalent Pfizer-BioNTech COVID-19 Vaccine is authorized to provide a three-dose primary series in individuals 6 months through 4 years of age. Authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) has been considered for the express purpose of improving protection conferred by the third dose of the primary series in individuals 6 months through 4 years of age against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit/risk balance compared to Pfizer-BioNTech COVID-19 Vaccine for the third dose. Consequently, at this time, revising this EUA to no longer provide for the use of the Pfizer-BioNTech COVID-19 Vaccine as a third dose in the primary series in this age group is appropriate for the protection of the public health. Accordingly, authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use as a third primary series dose in individuals 6 months through years of age would be accompanied by the revision of the authorization for the monovalent Pfizer-BioNTech COVID-19 Vaccine such that the monovalent vaccine would no longer be authorized for use as a third primary series dose for use in individuals 6 months through four years of age.

6 FDA Review of Post-Authorization Safety Data from Bivalent Booster Doses

As of November 30, 2022, more than 25 million doses of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) have been administered in the U.S. Among the U.S. population 5-11 years of age, 11,260,424 individuals have received a first mRNA COVID-19 vaccine dose, 9,240,747 have completed the primary series, and 631,222 have received an mRNA COVID-19 bivalent booster dose ([CDC COVID Data Tracker](#), accessed on December 5, 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 October 12, 2022) for use as a single booster dose among individuals ages ≥ 5 years. In the population of individuals 6 months through 4 years of age receiving the Pfizer-BioNTech COVID-19 Vaccine, as of November 30, 2022, a total of at least one vaccine has been administered to 1,005,583 individuals, and 296,328 of these have completed the three-dose Pfizer-BioNTech primary series (data provided by CDC's National Center for Immunization and Respiratory Diseases).

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event (AE) reports following administration of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) 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.

As of November 22, 2022, among individuals 5-11 years of age who were vaccinated with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) from August 31, 2022, through November 21, 2022, VAERS received 576 reports (575 U.S.), the majority (n=573, 99.5%) of which were non-serious reports. There were three serious reports (2 U.S., 1 foreign): 1) 6-year-old female who was recently treated for otitis externa and vaccinated with an influenza vaccine developed Miller Fisher syndrome with onset 3-days post-bivalent vaccination, respiratory pathogen panel was positive for rhinovirus and enterovirus, outcome unknown (U.S. report); 2) 7-year-old male developed diarrhea, pyrexia, and vomiting with onset the same day post-vaccination (U.S. report), outcome of recovering/resolving; and 3) 6-year-old male with history of COVID-19 less than 2 months prior to vaccination received an adult dose of vaccine and experienced reactive arthritis of the right hip with onset same day post-vaccination, outcome of ongoing at time of report (foreign report). Among individuals 5-11 years of age, the top ten most frequently reported MedDRA preferred terms* (PTs) for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) include:

- Most frequent PTs (Bivalent Vaccine, ages 5-11 years): incorrect dose administered, no adverse event, product administered to patient of inappropriate age, product preparation issue, incorrect product formulation administered, wrong product administered, product preparation error, pyrexia, pain in extremity, and fatigue.
- Most frequent non-medication errors PTs (Bivalent Vaccine, ages 5-11 years): pyrexia, pain in extremity, fatigue, headache, syncope, dizziness, pain, vomiting, injection site pain, nausea.

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

Safety concerns previously identified from post-authorization safety surveillance data in VAERS for the Pfizer-BioNTech COVID-19 Vaccine are summarized below for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Anaphylaxis, myocarditis, and pericarditis are existing safety concerns that have been added to the product Fact Sheets.

Anaphylaxis

Post-authorization surveillance for the 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.^{26,27} 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 November 28, 2022, there have been 17 U.S. reports of anaphylaxis/anaphylactoid reaction following receipt of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) among individuals of all ages (based on an automated search); there were no reports of anaphylaxis among individuals 5-11 years of age. 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 Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for all ages in the U.S. is 0.7 cases per million doses administered, which is similar to estimated rates for other vaccines.²⁸

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 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).²⁹ There were no verified reports of myocarditis/pericarditis following a first booster dose among individuals 5-11 years of age.²⁹ In addition, an automated query of the VAERS database run on November 28, 2022, did not return any reports of myocarditis/pericarditis following a bivalent booster dose among individuals 5-11 years of age.

Although some cases of vaccine-associated myocarditis/pericarditis following the 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 12-29 years of age, 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.²⁹ 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 and bivalent Pfizer-BioNTech COVID-19 Vaccine. The Sponsor is conducting additional post-authorization/ postmarketing 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 patterns suggesting new safety concerns for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Most AEs are labeled events, including anaphylaxis and myocarditis/pericarditis, and are consistent with the known safety profile for the original vaccine. In addition, the sponsor submitted a summary of post-authorization AE reports for the bivalent vaccine among individuals 5-11 years of age and for dose 3 of the original Pfizer-BioNTech COVID-19 Vaccine among individuals 6 months through 4 years of age. Review of the sponsor's data did not identify new clinical safety concerns. Medication errors were among the most commonly reported events (majority without co-reported clinical AEs) and the sponsor has employed mitigation strategies to address this risk. No unusual frequency, clusters, or other trends for AEs were identified that would suggest new safety concerns for the bivalent vaccine.

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

7.1 Chemistry, Manufacturing, and Controls (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 (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 3- μ g mRNA dose (1.5 μ g of each mRNA construct). Each bivalent dose also contains the following ingredients: a total lipid content of 0.075 mg (ALC-0315, ALC-0159, DSPC, and cholesterol), 0.006 mg tromethamine (Tris base), 0.04 mg tromethamine hydrochloride (Tris-HCl), 3.2 mg

sucrose and 1.52 mg sodium chloride (from diluent).

The 3- μ g mRNA dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is supplied as a multi-dose vial (MDV) filled at 0.4 mL fill volume. Each MDV requires dilution with 2.2 mL 0.9% sodium chloride prior to administration and 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 18 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 18-month shelf life.

The manufacturing process for the 3- μ g mRNA dose of the bivalent vaccine is essentially the same as that used for the previously authorized 30- and 10- μ g mRNA doses with the exception of the final fill volumes: 2.25 mL, 1.3 mL, and 0.4 mL for the 30-, 10- μ g, and 3- μ g doses supplied in multi-dose vials, respectively. Consistent manufacturing of the Pfizer-BioNTech COVID-19 Vaccine at the fill volume of 0.4 mL for the 3- μ g 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 3- μ g 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 3- μ g mRNA with acceptable quality.

The manufacture of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 6 months through 4 years of age is performed at existing facilities that were previously authorized under EUA for the manufacture of the original Pfizer-BioNTech COVID-19 Vaccine, and these facilities are currently authorized for the 30 μ g/dose and 10 μ g/dose bivalent vaccine. No changes were made to the facilities, equipment, container-closure systems, quality systems and controls. The Sponsor proposes to conduct manufacturing operations and controls as previously authorized for the original Pfizer-BioNTech COVID-19 Vaccine. 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) under an Emergency Use Authorization, including the presentation of the vaccine that is proposed for use in individuals 6 months through 4 years of age.

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 (Original and Omicron BA.4/BA.5) 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 (Original and Omicron BA.4/BA.5), including in individuals <12 years of age, in the following studies:

- 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.

- 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 (Original and Omicron BA.4/BA.5) modified vaccine.

- C4591051: A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 bivalent Omicron-modified vaccine in the United States

Objective: To assess the occurrence of safety events of interest, including myocarditis and pericarditis, following receipt of the Pfizer-BioNTech COVID-

19 bivalent Omicron-modified vaccine in the general U.S. population of all ages.

- C4591052: Post-authorization approval active surveillance study among individuals in Europe receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) bivalent Omicron-modified vaccine

Objective: To assess the potential increased risk of AESIs, including myocarditis/pericarditis, after being vaccinated with COVID-19 bivalent Omicron-modified vaccine, in all authorized age groups.

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.

In addition, because the primary series for individuals 6 months through 4 years of age is being revised to no longer consist of only monovalent doses, FDA is revising the scope of authorization for the Pfizer COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 5 years of age and older so that it can be administered as a booster dose regardless of whether primary vaccination was completed with a monovalent COVID-19 vaccine. Specifically, we are authorizing the Pfizer COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 5 years of age and older as a single booster dose

administered at least 2 months after either: 1) completion of primary vaccination with any FDA authorized or approved COVID-19 vaccine, or 2) receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine.

8 Benefit/Risk in the Context of the Proposed EUA For Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) For Use as a Third Primary Series Dose in Individuals 6 Months Through 4 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 98 million cases of COVID-19 and over 1 million deaths in the U.S. Since the start of the pandemic, there has been a succession of COVID-19 variants including Beta, Delta, Omicron BA.1, Omicron BA.5, and most recently Omicron BQ.1 and BQ1.1. Current treatment options for COVID-19 in individuals 6 months through 4 years of age include antiviral medications, convalescent plasma, and immune modulators approved or authorized for the management of individuals with COVID-19. 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 6 months through 4 years of age, the two mRNA-based vaccines from Moderna and Pfizer-BioNTech for use as a primary series. These monovalent vaccines are based on the original (ancestral) strain of SARS-CoV-2, and these vaccines initially had effectiveness of up to 90 to 95% against symptomatic disease when the ancestral strain was circulating. However, 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,^{30,31} Israel,¹⁹ Qatar,¹⁶ Portugal,³² and England.¹⁰

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 elicit an antibody response to BA.4 and BA.5 variants which is several-fold higher than the response elicited by the original (monovalent) vaccine.

Based on previous experience and available evidence, including safety, immunogenicity, and effectiveness data obtained with the monovalent Pfizer-BioNTech COVID-19 Vaccine in individuals 6 months through 4 years of age, vaccination with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) booster dose is expected to elicit a stronger immune response to the BA.4 and BA.5 variants. An initial study performed during the time

when BA.4 and BA.5 were circulating indicated that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was relatively more effective than an Original COVID-19 vaccine as booster dose in adults.² 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, including symptomatic and serious disease with the recently dominant Omicron BQ.1 and BQ.1.1 variants, and this uncertainty is likely to be even greater for 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 5-11 years of age, and 0.95 cases per 100,000 vaccine doses among male individuals 5-11 years of age (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 rate of myocarditis in individuals 6 months through 4 years of age is expected to be no higher, and perhaps may be lower, than that observed in the 5-11 year age group.

The totality of the available evidence indicates that replacing the third dose of the primary series for children 6 months through 4 years old with Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) will likely increase the immune response against SARS-CoV-2 variants and may particularly help better protect against the emerging Omicron variants such as BQ.1 and BQ.1.1. Administration of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) vaccine as the third dose of the primary series is appropriate for all individuals 6 months through 4 years of age when given at least two months after two previous Pfizer-BioNTech COVID-19 Vaccine primary series doses.

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	<ul style="list-style-type: none"> • COVID-19 caused by SARS-CoV-2 has been responsible for over 98 million cases and over 1 million deaths in the U.S. • There has been a succession of variants (including Delta, Omicron BA.1, BA.4, BA.5, BQ.1, BQ1.1, and other subvariants) 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 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Treatment options for individuals 6 months through 4 years of age are limited, especially for those under 2 years of age. • An antiviral medication, immune modulators, and convalescent plasma have been approved or authorized for the management of individuals with COVID-19 • There are currently two authorized mRNA COVID-19 vaccines for use as a primary series in individuals 6 months through 4 years of age 	<ul style="list-style-type: none"> • Currently available treatments may not prevent complications from COVID-19, including post-acute sequelae of COVID-19 (long COVID); 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	<ul style="list-style-type: none"> • 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 U.S. because of SARS-CoV-2 variant evolution • Non-clinical studies in mice indicate that a bivalent (Original and BA.4/BA.5) COVID-19 vaccine booster dose will elicit an antibody response against BA.4 and BA.5 that is several-fold higher than the original booster and that is a few-fold higher against the Omicron BQ.1 and BQ.1.1 variants. • Data obtained in adults when BA.5 was predominant indicates that the bivalent COVID-19 boosters are relatively more effective than the original boosters in preventing symptomatic COVID-19. • Uncertain how the immune response to use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as a third dose of the primary series in individuals 6 months through 4 years of age will translate into effectiveness against the currently circulating variants for COVID-19 outcomes, including symptomatic and serious disease. 	<ul style="list-style-type: none"> • The totality of the available evidence indicates that use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and BA.4/BA.5) as a third primary series dose will likely increase the broad immune response against SARS-CoV-2 variants and may particularly help target current variants derived from Omicron BA.5. • It is reasonable to conclude that replacing the third dose of the primary vaccination series for the Pfizer-BioNTech COVID-19 Vaccine with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) may be effective in preventing serious or life-threatening disease.

8.2 Conclusions Regarding Benefit-Risk

For individuals 6 months through 4 years of age, the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for the third dose in the three-dose primary series outweigh the known and potential risks, 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 mRNA COVID-19 vaccines outweigh their risks. During the current phase of COVID-19 caused largely by Omicron variants derived from the BA.5 lineage (BQ.1 and BQ.1.1), the replacement of the third primary series dose with the COVID-19 Vaccine, Bivalent is expected to have a favorable benefit-risk profile, potentially helping to restore protection against serious outcomes from COVID-19, and possibly reducing symptomatic disease that may be followed by debilitating post-acute COVID-19 syndrome.

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 replacement of the third current Pfizer-BioNTech COVID-19 Vaccine dose of the primary series for individuals 6 months through 4 years old with 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:
 - data on the safety, immunogenicity, and effectiveness of the three-dose primary series of the monovalent Pfizer-BioNTech COVID-19 Vaccine in individuals 6 months through 4 years of age,
 - clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated primary and booster vaccination with the original Pfizer- BioNTech COVID-19 Vaccine, including data on safety and immunogenicity,
 - 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,
 - non-clinical immunogenicity data from a study of BNT162b2 formulations containing an Omicron BA.4/BA.5 component
 - post-marketing safety surveillance data with primary series and booster doses of the original Pfizer-BioNTech COVID-19 Vaccine, and booster doses of the Pfizer COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).
 - observational effectiveness data from a study evaluating booster vaccination with currently authorized BA.4/BA.5-containing bivalent mRNA COVID-19 vaccines
- 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) as the third dose of the primary vaccination series following two doses of the Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including Omicron variant sublineages derived from 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 the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) as the third dose of the primary vaccination series following two doses of the Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks. Known and potential benefits include reduction in the risk of symptomatic COVID-19 and associated serious sequelae, including from COVID-19 due to Omicron variants derived from 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 against newer variants derived from Omicron BA.5 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, as new derivatives of Omicron BA.5 circulate. However, these uncertainties must be balanced against available evidence demonstrating waning protection from COVID-19 vaccine primary series and monovalent booster doses, decreased effectiveness of currently available monovalent COVID-19 vaccines against Omicron BA.5, from which BQ.1 and BQ.1.1 are derived, 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 Pfizer-BioNTech COVID-19 Vaccine recipients 6 months through 4 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 5 years of age and older. COVID-19 vaccines that contain an Omicron component are not currently approved or available for use in individuals 6 months through 4 years of age.
- Review of VAERS data and the Sponsor’s periodic safety reports, did not identify patterns suggesting new safety concerns for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Most AEs are labeled events, including anaphylaxis and myocarditis/pericarditis, and consistent with the known safety profile

for the original vaccine. In addition, the sponsor submitted a summary of post-authorization AE reports for the bivalent vaccine among individuals 5-11 years of age and for dose 3 of the original Pfizer-BioNTech COVID-19 Vaccine among individuals 6 months through 4 years of age. Review of the sponsor's data did not identify new clinical safety concerns. Medication errors were among the most commonly reported events (majority without co-reported clinical AEs) and the sponsor has employed mitigation strategies to address this risk. No unusual frequency, clusters, or other trends for AEs were identified that would suggest new safety concerns for the bivalent vaccine.

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 the third dose of the COVID-19 primary vaccination series for individual 6 months through 4 years. The revised Pfizer-BioNTech primary vaccination series for individuals 6 months through 4 years of age will therefore consist of the first two doses of the Pfizer-BioNTech COVID-19 Vaccine given at least 3 weeks apart followed by a third dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) at least 8 weeks later.

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