

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

### Identifying Information

Application Type	EUA Amendment
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Review Completion Date	September 11, 2023
Established Name/Names used during development	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)
Dosage Forms/Strengths and Route of Administration	A 0.3 mL suspension for intramuscular injection (for 6 months through 4 years) A 0.3 mL suspension for intramuscular injection (for 5 years through 11 years of age) (For dosing regimen, dose, and schedule, refer to section <a href="#">5.1</a> )
Intended Use for EUA	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Intended Population	Individuals 6 months through 11 years of age

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## 1 Executive Summary

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be an ongoing global health challenge. As of August 16, 2023, SARS-CoV-2 has led to over 770 million cases of coronavirus disease 2019 (COVID-19), including 7 million deaths worldwide, and has caused societal, economic, and healthcare system disruptions. COVID-19 vaccination has been a cornerstone of the pandemic response, as vaccines may provide protection against COVID-19. COVID-19 vaccinations have been estimated to have prevented tens of millions of deaths worldwide in the first year alone after COVID-19 vaccines became available in December 2020.<sup>1</sup>

The Pfizer-BioNTech COVID-19 Vaccine is a nucleoside-modified messenger RNA (mRNA) vaccine encoding the full-length spike (S) protein of the Original (Wuhan Hu-1) SARS-CoV-2 strain, hereafter referred to as Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). The Pfizer-BioNTech COVID-19 Vaccine, Bivalent contains mRNAs encoding the S-glycoprotein of Original and S-glycoprotein of SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 (Omicron BA.4/BA.5). For more details on the sequence of authorizations of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), refer to executive summary in [FDA Review Memorandum Dated April 18, 2023](#).

On April 18, 2023, FDA authorized the use of the Pfizer-BioNTech and Moderna bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines in all individuals 6 months of age and older allowing for use of a single dose in most adults and pediatric populations; two or three doses (based on the vaccine used) in the youngest pediatric populations; an additional dose for persons 65 years of age and older; and additional age-appropriate doses for persons with certain kinds of immunocompromise. The EUA actions resulted in FDA no longer authorizing use of monovalent Moderna and Pfizer-BioNTech COVID-19 vaccines (containing the mRNA encoding spike protein of Original SARS-CoV-2 virus) and certain uses of the approved COVID-19 vaccines in the United States (U.S.). For details, refer to [FDA Review Memorandum Dated April 18, 2023](#). On April 28, 2023, FDA authorized additional doses of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 6 months through 4 years of age with certain kinds of immunocompromise.

Although real-world effectiveness studies suggest that the current bivalent COVID-19 vaccines continue to provide some protection against circulating sublineages of Omicron, including XBB.1.5,<sup>2,3</sup> there appears to be an inverse relationship between the time since vaccination and vaccine effectiveness, such that bivalent COVID-19 vaccine effectiveness against Omicron sublineages appears to wane over time.<sup>2,3</sup> Additionally, studies indicate that neutralizing antibody titers induced by the current bivalent COVID-19 vaccines against XBB-related sublineages are lower relative to neutralizing antibody titers induced against the matched BA.4/BA.5 sublineage.<sup>4</sup> These data suggest that an updated strain composition of COVID-19 vaccines to more closely match currently circulating Omicron sublineages is warranted.<sup>4</sup>

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) has convened in open session to discuss and make recommendations on the selection of strain(s) to be included in updated COVID-19 vaccines. On June 15, 2023, VRBPAC voted to recommend an update of the current COVID-19 vaccine composition to a monovalent XBB-lineage, with preference for the XBB.1.5 sublineage. FDA subsequently advised manufacturers updating their COVID-19

vaccines to develop vaccines with a monovalent XBB.1.5 composition for the 2023-2024 Formula (refer to section [3.2](#)).

Pfizer/BioNTech, on June 23, 2023, requested authorization of their COVID-19 vaccine to include 2023-2024 Formula as a 3-dose series at 3 µg in individuals 6 months to <5 years of age and as a single dose at 10 µg in individuals 5 to <12 years of age (refer to section [5](#)). Pfizer/BioNTech also requested authorization for use of additional doses in individuals with certain kinds of immunocompromise in 6 months through 11 years of age.

Given that the Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula) is manufactured using the same process as Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), postmarketing safety data for Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, Bivalent were considered relevant to the safety evaluation of the Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula). Review of postmarketing safety data indicate a similar safety profile of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). According to the last release of COVID-19 vaccine administration data by CDC on May 11, 2023, more than 366 million doses of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and more than 36 million doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) have been administered in the U.S. Of the total doses of either the original or bivalent COVID-19 vaccines given in the U.S., more than 3 million doses have been administered to individuals 6 months through 4 years of age and more than 22 million have been administered to individuals 5 through 11 years of age.

In recipients of all doses of Pfizer-BioNTech COVID-19 vaccines (Original monovalent and Bivalent) among children 6 months to less than 12 years of age, the most frequently reported preferred terms (PTs) reported to the Vaccine Adverse Event Reporting System (VAERS) were incorrect dose administered, product preparation issue, expired product administered, product administered to patient of inappropriate age, product storage error, pyrexia, incorrect product formulation administered, vomiting, headache, and fatigue. Of the important risks identified in the pharmacovigilance plan for Pfizer-BioNTech COVID-19 Vaccine, anaphylaxis and myocarditis/pericarditis are identified risks that are included in product labeling. The Sponsor is conducting additional safety-related post-authorization/postmarketing studies for the Pfizer-BioNTech COVID-19 Vaccine, including postmarketing requirement (PMR) studies to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. The Sponsor is also conducting post-authorization studies to evaluate the association between the Pfizer-BioNTech COVID-19 Vaccine and a pre-specified list of adverse events of special interest (AESIs) in all authorized ages in the general U.S. population (refer to section [7](#) for details).

The safety and effectiveness data accrued with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are relevant to Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), because all these vaccines are manufactured using the same process. The nonclinical data reviewed indicate that Pfizer-BioNTech Vaccine (2023-2024 Formula), when used in vaccine naïve or experienced laboratory animals, elicited higher neutralizing antibodies compared with the bivalent vaccine (Original and Omicron BA.4/BA.5) against XBB-related sublineages. Based on the totality of the available evidence (reviewed in detail in sections [6](#) and [7](#)), it is reasonable to expect that in immunocompetent and immunocompromised individuals 6 months through 11 years of age the Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula) compared with

Pfizer-BioNTech COVID-19 Vaccine (Original and Omicron BA.4/BA.5) will likely increase immune responses and clinical protection against COVID-19 caused by SARS-CoV-2 variants, including the currently predominant Omicron sublineages.

Taken together, the review team recommends: 1) discontinuation of use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent, (Original and Omicron BA.4/BA.5) in the U.S.; and 2) use of age-appropriate doses and dosing schedules of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) in individuals 6 months through 11 years of age, based on previous vaccination status, and immune competence.

## **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 coronavirus disease 2019 (COVID-19), an infectious disease with variable respiratory and systemic manifestations. As of August 16, 2023, SARS-CoV-2 infection has resulted in over 770 million cases of COVID-19 and an estimated 7 million deaths worldwide.<sup>5</sup> Disease symptoms vary. Many individuals present with asymptomatic or mild disease, while others, especially individuals 65 years of age and older and individuals with certain co-morbid conditions,<sup>6</sup> may develop severe respiratory tract disease, including pneumonia and acute severe respiratory distress syndrome, that leads to multiorgan failure and death. Most adults with COVID-19 recover within 1 to 2 weeks; however, symptoms may persist for months in some individuals.<sup>7</sup> Symptoms associated with SARS-CoV-2 infection in children are similar to those in adults but are generally milder, with fever and cough most commonly reported.<sup>5</sup> However, since the January 2022 surge in cases due to Omicron BA.1, rates of COVID-19-associated hospitalizations among infants younger than 6 months old are similar to those of adults ages 65 to 74 years old.<sup>8</sup>

In the U.S., more than 6.3 million COVID-19-associated hospitalizations and 1.1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).<sup>9</sup> Individuals 65 years of age and older accounted for approximately 14% of cases and 76% of deaths.<sup>10</sup> By contrast, individuals 18 years of age and younger represent 17% of COVID-19 cases and less than 0.3% of deaths.<sup>10</sup> Since the start of the pandemic, 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. COVID-19 vaccines based on the Wuhan-HU-1 strain of SARS-CoV-2 (also referred to as ancestral, reference or original strain) were launched in the U.S, starting in December 2020. Recent surges, both globally and in the U.S., have been associated with rapid spread of highly transmissible SARS-CoV-2 variants, most recently the Omicron variant of concern. Bivalent COVID-19 (Original and Omicron BA.4/BA.5) vaccines were deployed in the U.S. starting in September 2022.

The SARS-CoV-2 Omicron variant has continued evolving into distinct sublineages with additional mutations in the spike gene, as well as elsewhere in the genome. This has led to successive waves of many Omicron sublineages across the globe. In the U.S., BA.5 sublineage dominated during much of fall 2022, while other Omicron sublineages, including BA.4 sublineage, co-circulated at lower frequencies. Because BA.5 and BA.4 sublineages share the same spike mutations, the global dominance of BA.5 indicates that mutations in non-spike

genes contributed to its fitness advantage. BA.5 sublineages, like the earlier BA.1 Omicron sublineages, were much less susceptible to neutralization by post-vaccination (with Original strain vaccines) and post-infection sera compared to the pre-Omicron variants.

By winter of 2022, BQ sublineages diverged from BA.5 by acquiring additional mutations in the spike receptor binding domain (RBD), resulting in K444T, N460K, and R346T (BQ.1.1) substitutions. These changes conferred additional immune escape from post-vaccination and post-infection antibody responses. By spring 2023, BQ sublineages were rapidly replaced by XBB sublineages, both in the U.S. and globally. The XBB parent lineage resulted from a recombination of BA.2.10.1 and BA.2.75 sublineages, highlighting the relevance of recombination in generating new variants of concern. Recombination can occur during virus replication in cells infected by more than one variant.

XBB sublineages have continued to emerge that have accumulated a small number of mutations in the spike N-terminal domain and the receptor binding domain (RBD). The XBB.1.5 sublineage spread globally in the first quarter of 2023, reaching dominance in North America, as well as other parts of the world, by April. Compared to the parental XBB lineage virus, XBB.1.5 has two amino acid substitutions, G252V and S486P, in the RBD of the SARS-CoV-2 spike protein. These changes may confer additional growth advantage, likely due in part to increased affinity of the spike protein to the ACE2 receptor conferred by the S486P change.<sup>11</sup> Two additional Omicron sublineages, XBB.1.9 and XBB.1.16, have co-circulated with XBB.1.5.<sup>11</sup> The XBB.1.9 variant has the same spike protein sequence as XBB.1.5, but has a mutation in the Orf9b gene that may alter virus-host interactions to increase viral fitness.<sup>4,12</sup> Orf9b mutations have emerged in other sublineages, including XBB.1.16. From February to April 2023 the XBB.1.16 sublineages surged in India, quickly dominating other variants. Compared with the parental XBB lineage virus, XBB.1.16 has four spike substitutions, i.e., E180V, G252V, K478R, and S486P. XBB.1.16 is reported to have a higher reproductive number compared to XBB.1 and XBB.1.5, and the proportion of XBB.1.16 viruses rose rapidly in many other countries, including the U.S. Preliminary reports have indicated that no further immune evasion result from these substitutions in the XBB.1.16 spike protein compared with XBB.1.5.<sup>13,14</sup> Overall, XBB sublineages accounted for >95% of the circulating virus variants in the U.S. by early June 2023; at this time (August 2023), other circulating variants worldwide include XBB.1.9, XBB.2.3, and EG.5., FL1.5.1, CH1.1, BA.2.75 and BA.2.86. The dominant variant in the U.S. in late August 2023 was EG.5. EG.5 carries an additional F456L amino acid substitution in the spike protein compared to the parent XBB.1.9.2 subvariant and XBB.1.5. Within the EG.5 lineage, the subvariant EG.5.1 has an additional spike protein substitution Q52H and represents 88% of the available sequences for EG.5 and its descendent lineages.<sup>15</sup>

SARS-CoV-2 evolution is complex and remains unpredictable. Though acquired immunity through infection, vaccination, or both may abate severe clinical outcomes of COVID-19, there is no indication that SARS-CoV-2 evolution is slowing. Intrinsic viral factors, e.g., mutation rate and recombination potential, generate possibilities for increased transmissibility and adaptation to the host. Concurrently, host immune responses and other non-viral factors contribute to selection of variants. Generation of immune escape variants may be further facilitated by chronic infections in persons with weakened immune systems or potentially by waning of immunity in healthy immunocompetent individuals. Thus far, the impressive plasticity, especially in the SARS-CoV-2 spike protein, suggests that the virus can continue evolving by both incremental (drift-like) and saltatory (shift-like) modes, underscoring the importance of on-going global surveillance and ongoing assessments of the need to update preventive and therapeutic interventions.

## **2.2 Authorized and Approved Vaccines and Therapies for COVID-19**

Two COVID-19 vaccines are currently FDA approved for active immunization to prevent COVID-19 caused by SARS-CoV-2 for use in individuals 12 years of age and older. Three vaccines are currently authorized for use in the U.S. under emergency use authorization (EUA).

### **2.2.1 Comirnaty (2023-2024 Formula) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)**

Comirnaty (COVID-19 Vaccine, mRNA) (2023-2024 Formula) manufactured by Pfizer for BioNTech, is approved for use as a single dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Comirnaty contains a mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5). 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 currently authorized under EUA for administration of a single dose in individuals 5 years of age and older, three doses in individuals 6 months through 4 years of age previously not vaccinated with a COVID-19 vaccine, two doses if previously vaccinated with one dose of Pfizer-BioNTech COVID-19 Vaccine, or a single dose in individuals 6 months through 4 years of age previously vaccinated with two or three doses of Pfizer-BioNTech COVID-19 Vaccine. An additional dose is authorized for individuals 65 years of age and older at least 4 months after the first dose of a bivalent COVID-19 vaccine. Additional age-appropriate doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent are authorized for individuals with certain kinds of immunocompromise 6 months of age and older.

### **2.2.2 Spikevax (2023-2024 Formula) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)**

Spikevax (COVID-19 Vaccine, mRNA) (2023-2024 Formula) manufactured by Moderna, is approved for use as a single dose for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Spikevax (Original monovalent) contains nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized full-length spike (S) protein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5). A bivalent formulation of the vaccine manufactured using the same process, Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), is currently authorized under EUA for administration of a single dose in individuals 6 years of age and older, two doses in those individuals 6 months through 5 years of age previously not vaccinated with a COVID-19 vaccine and a single dose in individuals 6 months through 5 years of age previously vaccinated with Moderna COVID-19 Vaccine. An additional dose is authorized for individuals 65 years of age and older at least 4 months after the first dose of a bivalent COVID-19 vaccine. Additional age-appropriate doses of Moderna COVID-19 Vaccine, Bivalent are authorized for individuals with certain kinds of immunocompromise 6 months of age and older.

### **2.2.3 Novavax COVID-19 Vaccine, Adjuvanted**

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, and as a first booster dose in the following individuals: Individuals 18 years and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate, and 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. For additional information on dosing and schedule, please refer to the [Fact Sheet](#). Safety and

effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the [FDA website](#).

## **2.2.4 Therapies for COVID-19**

### **2.2.4.1 FDA-approved therapies for COVID-19**

#### Oral antivirals:

Veklury (remdesivir) is approved for the treatment of COVID-19 in adults and pediatric patients ( $\geq 28$  days old and weighing  $\geq 3$  kg), who are:  
Hospitalized; or Not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

#### Immune modulators:

Olumiant (baricitinib) is approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Actemra (Tocilizumab) is approved for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

### **2.2.4.2 Emergency use authorized pharmacological products for pre-exposure prophylaxis of COVID-19, post-exposure prophylaxis and/or treatment of COVID-19**

#### Oral antivirals:

Paxlovid ([nirmatrelvir tablets; ritonavir tablets], co-packaged for oral use) is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.

Lagevrio (molnupiravir) is authorized for the treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19):

- who are at high risk for progression to severe COVID-19, including hospitalization or death, and for
- whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

#### SARS-CoV-2-targeting monoclonal antibodies:

Several SARS-CoV-2-targeting monoclonal antibodies have been authorized under EUA but are not currently authorized due to the high frequency of circulating SARS-CoV-2 variants that are non-susceptible to them (For detail of previously authorized SARS-CoV-2-targeting monoclonal antibodies, please refer to section 2.2.5 of the [FDA Review Memorandum Dated April 18, 2023](#)).

#### Immune modulators:

Kineret (anakinra) is authorized for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental



oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).

Gohibic (vilobelimab) is authorized for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation (IMV), or ECMO.

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 ECMO.

Tocilizumab is authorized for the treatment of COVID-19 in hospitalized 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:

COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in either the outpatient or inpatient setting.

### **3 Rationale for Strain Change**

#### **3.1 Current Effectiveness of Authorized Bivalent COVID-19 Vaccines and Need for a Strain Update**

Following emergence of the Omicron variant and its sublineages (BA.1, BA.4/BA.5, and related sublineages) in November 2021, and based on immunogenicity data suggesting improved protection against Omicron sublineages conferred by bivalent COVID-19 vaccines (Original and Omicron BA.1) compared to the original monovalent COVID-19 vaccines, FDA, on August 31, 2022, authorized use of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for booster doses in individuals 18 or 12 years of age and older, respectively, and revised the scope of authorization for these manufacturers' monovalent vaccines to remove their use as a booster dose in those age groups for which a bivalent booster was authorized. Subsequently, FDA also authorized use of the respective bivalent vaccines for booster doses for younger age groups and removed authorization of the monovalent Pfizer-BioNTech COVID-19 Vaccine as a booster dose in individuals 5 through 11 years of age when the Pfizer-BioNTech COVID-19 Vaccine, Bivalent was authorized as a booster in that age group.

Subsequent to the authorizations of the bivalent mRNA COVID-19 vaccines as boosters in children and adults, observational data indicated that the bivalent COVID-19 vaccines provided improved protection from COVID-19 caused by sublineages of Omicron, including the BA.4/BA.5 sublineage, compared to the original monovalent vaccines.<sup>16-22</sup> The improved protection against circulating variants provided by the bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines compared with the original monovalent COVID-19 vaccines provided support for the transition to use of bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines for all doses for mRNA COVID-19 vaccines authorized in individuals 6 months of age and older as well as support for periodic updates of the strain composition of COVID-19 vaccines. In addition, based on the totality of available scientific evidence, FDA concluded that it was reasonable to expect that bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines administered as a single dose to all individuals (unvaccinated or vaccinated) in the U.S. 5 (Pfizer-BioNTech COVID-19 Vaccine, Bivalent) or 6 (Moderna COVID-19 Vaccine, Bivalent)

years of age and older at least 2 months following any prior monovalent COVID-19 vaccine dose, 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 and other Omicron subvariants, such as XBB.1.5.

In April 2023, FDA authorized use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for all doses for individuals 6 months of age and older. A single dose regimen of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was authorized for individuals 5 or 6 years of age and older, respectively. An additional dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) was authorized for individuals 65 years of age and older. Additional doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) were authorized for individuals with certain kinds of immunocompromise.

SARS-CoV-2 continues to evolve into distinct sublineages by acquiring additional mutations (see section 2.1). Although real-world effectiveness studies suggest that the current bivalent vaccines continue to provide protection against currently circulating sublineages of Omicron, including XBB.1.5,<sup>2,3</sup> there appears to be an inverse relationship between the time since vaccination and vaccine effectiveness, such that bivalent COVID-19 vaccine effectiveness against Omicron sublineages appears to wane over time. Additionally, studies indicate that neutralizing antibody titers induced by the current bivalent COVID-19 vaccines against XBB-related sublineages are lower relative to neutralizing antibody titers induced against the matched BA.4/BA.5 sublineage.<sup>4</sup> These data suggest that an updated strain composition of COVID-19 vaccines to match more closely the currently circulating Omicron sublineages is warranted.

### **3.2 Recommendation for the 2023-2024 Formula of COVID-19 Vaccines in the U.S.**

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) has periodically convened in open session to discuss and make recommendations on the selection of strain(s) to be included in updated COVID-19 vaccines. At the January 26, 2023, VRBPAC meeting on COVID-19 vaccines, FDA stated that it anticipates assessing SARS-CoV-2 evolution at least annually (review of data to commence in the spring of each year) and to convene the VRBPAC in June of each year regarding strain selection for fall vaccination.

Data on SARS-CoV-2 evolution indicated that XBB sublineages accounted for more than 95% of the circulating virus variants in the U.S. as of early June 2023. While XBB.1.5 had declined to less than 40% of presumed circulating virus in the U.S., XBB.1.16 was on the rise and XBB.2.3 was slowly increasing in proportion (CDC COVID Data Tracker: Variant Proportions). The trajectory of virus evolution suggested that XBB.1.16 could be dominant by fall 2023. XBB.2.3 and other XBB sublineages could also continue to increase in proportion as the virus evolved. Although SARS-CoV-2 continues to evolve, the amino acid sequences of XBB.1.5, XBB.1.16, and XBB.2.3 spike protein appear similar, with few amino acid differences. Available evidence suggests little to no further immune evasion from these new amino acid substitutions in the XBB.1.16 spike protein compared to XBB.1.5. By several measures, including escape from antibody neutralization and waning protection, the currently available bivalent COVID-19 (Original and Omicron BA.4/BA.5) vaccines appear less effective against currently circulating variants (e.g., XBB-lineage viruses) than against previous strains of SARS-CoV-2. The totality of

available evidence suggests that an update to the composition of COVID-19 vaccine to a monovalent XBB-lineage vaccine is warranted for 2023–2024.

The VRBPAC met on June 15, 2023, to discuss the strain composition for the 2023-2024 Formula of COVID-19 vaccines in the U.S. Sublineages considered by the VRBPAC included XBB.1.5, XBB.1.16, and XBB.2.3. Evidence influencing strain selection discussed by the Committee included virus surveillance and genomic analyses, antigenic characterization of viruses, human serology studies from current vaccines, pre-clinical immunogenicity studies evaluating immune responses generated by candidate vaccines. The Committee also reviewed manufacturing timelines.

For the 2023-2024 Formula of COVID-19 vaccines in the U.S., the committee unanimously voted in favor (21 Yes and 0 No votes) of recommending a 2023-2024 Formula update of the current vaccine composition to a monovalent XBB-lineage. Based on the evidence and other considerations presented, committee members expressed a preference for selection of XBB.1.5 for the 2023-2024 Formula. Based on the totality of the evidence, FDA advised manufacturers seeking to update their COVID-19 vaccines that for the 2023-2024 Formula of COVID-19 vaccines in the U.S. they should develop vaccines with a monovalent XBB.1.5 composition.

#### **4 Regulatory Considerations for EUA of a Bivalent COVID-19 Vaccine with an Omicron Component**

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

The Secretary of the U.S. Department of Health and Human Services (HHS) has determined that there is a public health emergency or a significant potential for a public health emergency, that affects, or has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves the virus that causes COVID-19. Based on that determination, and the Secretary's declaration that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, 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 expectations.

#### **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 monovalent vaccine to address emerging SARS-CoV-2 variants. With respect to clinical data, the guidance recommends clinical evaluation of modified monovalent vaccines, while also recognizing that FDA's thinking regarding data needed to authorize a modified COVID-19 vaccine may evolve as additional information is accrued with SARS-CoV-2 variants and corresponding vaccines. Although the authorization of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is not supported by clinical studies of the 2023-2024 formulation vaccine, FDA's thinking about the need for such data has evolved since issuance of the guidance. Based upon the accumulated experience with the Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and BA.4/BA.5) (see Section 6), it is reasonable to conclude that clinical studies of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) are not necessary to support issuance of an EUA. The experience with the Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and BA.4/BA.5), combined with the CMC and preclinical data submitted as part of the EUA request, support a favorable benefit-risk profile for the uses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) that are under consideration.

### **5 EUA Amendment Request to Include the 2023-2024 Formula for Pfizer-BioNTech COVID-19 Vaccine**

#### **5.1 Summary of the EUA Request**

Following the June 15, 2023, VRBPAC discussion and FDA's advice to manufacturers updating their vaccines to develop vaccines with a monovalent XBB.1.5 composition (section 3.2), Pfizer/BioNTech, on June 23, 2023, requested authorization of their COVID-19 vaccine to include the 2023-2024 Formula as a 3-dose primary series at 3 µg (provided in a dilute-to-use multidose vial [3-dose presentation after dilution]) in individuals 6 months to <5 years of age and as a single dose at 10 µg (provided as a ready-to-use single dose vial) in individuals 5 to <12 years of age based upon:

- Preclinical data that support the strain selection
- 2023-2024 Formula vaccine 3-µg and 10-µg-specific CMC packages provided in Module 3 of the EUA request.

The request includes an update to the dose and administration schedule for Pfizer-BioNTech COVID-19 Vaccine, 2023-2024 Formula, consistent with the following tables.

**Table 1. Individuals 6 Months Through 4 Years of Age by Pfizer-BioNTech COVID-19 Vaccination Status**

<b>Number of Previous Doses of Pfizer-BioNTech COVID-19 vaccine(s)<sup>a</sup></b>	<b>Pfizer-BioNTech COVID-19 Vaccine, (2023-2024 Formula) Vial Cap and Label Border Color</b>	<b>Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) Dosing Regimen, Dose and Schedule<sup>b</sup></b>
0 <sup>c</sup>	Yellow	3 doses <sup>d</sup> , 0.3 mL each Dose 1: Week 0 Dose 2: Week 3 Dose 3: ≥8 weeks after Dose 2
1	Yellow	2 doses <sup>d</sup> , 0.3 mL each Dose 1: 3 weeks after receipt of the previous dose of Pfizer-BioNTech COVID-19 vaccine <sup>a</sup> Dose 2: ≥8 weeks after Dose 1
2 to 4	Yellow	Single dose, 0.3 mL ≥8 weeks after receipt of the last previous dose of Pfizer-BioNTech COVID-19 vaccine <sup>a</sup>

a. Previous doses of Pfizer-BioNTech COVID-19 vaccine(s) refers to doses with Pfizer-BioNTech COVID-19 Vaccine (original monovalent) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

b. For individuals with certain kinds of immunocompromise previously vaccinated with Pfizer-BioNTech COVID-19 vaccines, see text below tables for dosing information.

c. Not previously vaccinated with any COVID-19 vaccine.

d. Individuals turning from 4 to 5 years of age during the vaccination series should receive all doses with Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) supplied in vials with yellow caps and labels with yellow borders.

**Table 2. Individuals 5 Years Through 11 Years of Age Irrespective of COVID-19 Vaccination Status**

<b>Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) Vial Cap and Label Border Color</b>	<b>Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) Dosing Regimen, Dose and Schedule<sup>a</sup></b>
Blue	Single dose, 0.3 mL ≥2 months after receipt of the previous dose of COVID-19 vaccine <sup>b</sup>

a. For individuals with certain kinds of immunocompromise, see text below tables for dosing information.

b. COVID-19 vaccine refers to the monovalent COVID-19 vaccines that encode the spike protein of the original SARS-CoV-2 and the bivalent COVID-19 vaccines encoding the spike protein of original SARS-CoV-2 and of the Omicron variant lineages BA.4 and BA.5.

### Dosing Schedule for Immunocompromised

Individuals with certain kinds of immunocompromise<sup>a</sup> 6 months through 11 years of age should complete at least a three-dose series with an age-appropriate dose and dosing schedule<sup>b,c</sup> of a COVID-19 vaccine. At least 1 dose should be with a COVID-19 vaccine (2023-2024 Formula).

- If previously not vaccinated, complete the three-dose series with age-appropriate doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).
- If previously vaccinated with one or two dose(s) of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and/or the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron

<sup>a</sup> Certain kinds of immunocompromise refers to individuals who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

<sup>b</sup> Dosing schedule for individuals 6 months through 4 years of age for Pfizer-BioNTech COVID-19 vaccines: Dose 1: Week 0; Dose 2: Week 3; Dose 3: ≥8 Weeks after Dose 2. For individuals turning from 4 to 5 years of age during the vaccination series, complete the series with doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) supplied in vials with yellow caps and labels with yellow borders.

<sup>c</sup> Dosing schedule for individuals 5 through 11 years of age for Pfizer-BioNTech COVID-19 vaccines: Dose 1: Week 0; Dose 2: Week 3; Dose 3: ≥4 weeks after Dose 2. Individuals turning from 11 to 12 years of age during the vaccination series may complete the series with doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) supplied in vials with blue caps and labels with blue borders.

BA.4/BA.5), complete the remaining dose(s) in the three-dose series with age-appropriate doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).

- If previously vaccinated with three or more doses, administer a single age-appropriate dose of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) at least two months following the last previous dose.<sup>d,e</sup>

An age-appropriate additional dose of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) may be administered at least 2 months following the last dose of a COVID-19 vaccine (2023-2024 Formula).<sup>f,9</sup> Age-appropriate additional doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) may be administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances. The timing of the additional doses may be based on the individual's clinical circumstances.

## 5.2 FDA's Approach for Selection of Strains to be Included in 2023-2024 Formula for COVID-19 Vaccines

In previous discussions with the VRBPAC, FDA described the proposed evidentiary basis that would be used to determine the need for updating the strain composition of COVID-19 vaccines. The relevant data reviewed would ideally include multiple types and sources. FDA reviewed various types of data as listed below, engaged with the key partners generating such data, including vaccine manufacturers and other U.S. government agencies, and reviewed the discussions and recommendations by other regulatory groups and public health agencies related to COVID-19 vaccine strain composition for 2023-2024.

- **Virus surveillance and genomic analyses to identify emerging new virus variants.** As described in section [2.1](#), SARS-CoV-2 XBB-lineage viruses currently predominate in the U.S. and globally.
- **Antigenic characterization of viruses to identify antigenically distinct variant viruses.** As described in section [2.1](#), SARS-CoV-2 XBB-lineage viruses have numerous amino acid changes relative to previously circulating SARS-CoV-2 viruses and the strains used in the authorized bivalent COVID-19 vaccines, suggesting continued evolution and increasing immunological distance from the Omicron BA.4/BA.5 component of currently authorized COVID-19 mRNA vaccines.
- **Post-vaccination human serology studies to evaluate antibody responses generated by the current vaccines against more recently circulating virus variants such as XBB-lineage viruses.** Since COVID-19 vaccine manufacturers are best positioned to generate the robust data needed from post-vaccination human serology studies, FDA set up informal technical working group meetings with each of the manufacturers of currently authorized/approved COVID-19 vaccines to share and discuss findings from human serology studies of their current vaccines against current circulating viruses. These data were presented at the June 2023 VRBPAC by the vaccine manufacturers.
- **Pre-clinical immunogenicity studies to evaluate immune responses generated by new candidate vaccines (e.g., expressing or containing updated variant spike components) against antigenically distinct circulating virus variants.** Pre-clinical

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<sup>d</sup> For immunocompromised individuals 6 months through 4 years of age, the last previous dose refers to the last dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), which are no longer authorized for use in the U.S.

<sup>e</sup> For immunocompromised individuals 5 through 11 years of age, the last previous dose refers to the last dose of a COVID-19 vaccine (Original monovalent) or bivalent COVID-19 vaccine, which are no longer authorized for use in the U.S.

<sup>f</sup> For immunocompromised individuals 6 months through 4 years of age, the last dose of a COVID-19 vaccine (2023-2024 Formula) refers to a dose with Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).

<sup>9</sup> For immunocompromised individuals 5 through 11 years of age, the last dose of a COVID-19 vaccine (2023-2024 Formula) refers to a dose with Moderna COVID-19 Vaccine (2023-2024 Formula) or Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).

immunogenicity data (neutralizing antibody) can provide an indication of how well antibodies to the spike protein of one strain will cross-neutralize other variant strains of SARS-CoV-2. These data help inform strain selection in combination with other data. As with human serology studies, COVID-19 vaccine manufacturers are also able to generate pre-clinical immunogenicity studies with new candidate vaccines and each of the manufacturers of authorized/approved COVID-19 vaccines has produced several candidate vaccines at risk and evaluated them in pre-clinical studies. These data were also presented at the June 2023 VRBPAC by the vaccine manufacturers.

### **5.3 Basis for EUA Revision to Remove Authorization for Use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in the U.S. and Clarify Export and Other Conditions**

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).

Circumstances currently exist that make appropriate a revision of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA5) EUA to protect the public health. As outlined in Section [2.2](#), the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA5) is authorized for use in individuals 6 months of age and older. Authorization of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), for individuals 6 months through 11 years of age, as described in the EUA request, is being considered for the express purpose of improving protection against the currently circulating SARS-CoV-2 Omicron sublineages, resulting in a more favorable anticipated benefit-risk profile for the Moderna COVID-19 Vaccine (2023-2024 Formula). FDA has also approved a supplemental biologics license application for COMIRNATY (2023-2024 Formula), which contains mRNA encoding the viral spike (S) glycoprotein of Omicron XBB.1.5, for active immunization to prevent COVID-19 in individuals 12 years of age and older. In addition, revising the EUA to remove the authorization of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA5) for use in the U.S. ensures that vaccination programs will continue to use a single current formula (i.e., 2023-2024 Formula) for Pfizer-BioNTech's COVID-19 vaccines, which should continue to help minimize vaccine administration errors that would result from availability of multiple different vaccine formulas and also potentially encourage vaccine uptake. Consequently, at this time, revising the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA5) EUA to remove its authorization for use in the U.S. is appropriate to protect the public health.

That said, the considerations about the U.S. vaccination programs are not applicable when the vaccine is used in other countries, and existing supplies of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) may continue to be available for export. FDA continues to conclude that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) outweigh the known and potential risks, when used in accordance with the current authorization. In addition, all other requirements in section 564(c) of the FD&C Act continue to be met with respect to the uses for which the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) is currently authorized. Therefore, it is appropriate to continue to authorize the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for export.

Accordingly, authorization of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) for use in individuals 6 months through 11 years of age as described in the EUA request, would be accompanied by the revision of the authorization for the Pfizer-BioNTech COVID-19 Vaccine,

Bivalent (Original and Omicron BA.4/BA.5) to remove its authorization for use in the U.S. in all age groups but permit its continued export under the EUA, subject to specific conditions. These conditions include, among other things, that the regulatory authorities of the countries in which the vaccine will be used are informed that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and associated Fact Sheets are no longer authorized for use in the U.S. and that FDA is no longer revising those Fact Sheets with updated information. These conditions also include a requirement to provide the regulatory authorities, upon request, with the currently authorized Fact Sheets. These conditions will ensure that the regulatory authorities in destination countries have relevant information with respect to the vaccine.

Previously, FDA's EUA required the distribution of the Pfizer-BioNTech COVID-19 vaccines to emergency response stakeholders at the direction of the U.S. government as a condition necessary or appropriate to protect the public health. Due to changed circumstances, we conclude that this limitation on distribution is no longer necessary or appropriate to protect the public health. Whereas there was previously a need for the U.S. government to coordinate distribution across federal, state, and local government entities to ensure appropriate allocation of the vaccines, this is no longer the case. In addition, we are no longer requiring all vaccination providers administering COVID-19 vaccine to be enrolled in the CDC COVID-19 Vaccination Program, as CDC no longer plans for that program to apply to all vaccination providers and this requirement is no longer necessary or appropriate to protect the public health.

## **6 FDA Review of Clinical Effectiveness and Safety Data**

### **6.1 Overview of Clinical Studies**

The effectiveness data accrued with the Pfizer-BioNTech COVID-19 Vaccine (no longer authorized for use in the U.S.) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are relevant to Pfizer-BioNTech COVID-19 Vaccine, (2023-2024 Formula) because these vaccines are manufactured using the same process. A high-level summary of previously reviewed data that support the effectiveness of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) for individuals 6 months through 11 years of age is provided below.

#### **6.1.1 Effectiveness of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)**

The effectiveness of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) in individuals 6 months through 11 years of age is based on:

- Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in individuals 6 months of age and older, and
- Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in individuals 6 months through 4 years of age

based on the following evidence (for detailed review of the evidence, please refer to section 6.2 and 6.3 of the [FDA Review Memorandum Dated April 18, 2023](#)):

- Efficacy of 2-Dose Primary Series of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in Participants 16 Years of Age and Older
- Efficacy of 2-Dose Primary Series of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in Participants 12 Through 15 Years of Age
- Efficacy of 2-Dose Primary Series of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in Participants 5 Through 11 Years of Age



- Immunogenicity of 2-Dose Primary Series of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in Participants 5 Through 11 Years of Age
- Effectiveness of 3-Dose Primary Series of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in Participants 6 Months Through 4 Years of Age
- Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) Booster Dose Following Pfizer-BioNTech COVID-19 Vaccine (Original Monovalent) Primary Series in Participants 5 Through 11 Years of Age
- Immunogenicity of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) Booster Dose Following Primary Vaccination with Another Authorized or Approved COVID-19 Vaccine (Original monovalent)
- Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) Administered as a Booster (Fourth Dose) in Individuals 6 Months Through 4 Years of Age
- Effectiveness of a Single Dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) in Individuals with Evidence of Prior SARS-CoV-2 Infection

### **6.1.2 Immunocompromised Individuals**

The effectiveness of Pfizer-BioNTech COVID-19 Vaccine three-dose series in individuals 6 months through 11 years of age with certain kinds of immunocompromise is inferred from immunogenicity of third primary series dose in individuals with certain kinds of immunocompromise (For detailed review of the evidence, please refer to [August 12, 2021, Review Memorandum](#).)

The effectiveness of additional doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) for immunocompromised individuals 6 months through 11 years of age is inferred from the following evidence (for detailed review of the evidence, please refer to sections of the [FDA Review Memorandum Dated April 18, 2023 listed below](#)):

- Immunogenicity of a Fourth Dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) after Completion of Primary Vaccination with 3 doses of the Pfizer BioNTech COVID-19 Vaccines in Individuals 6 months through 4 years of age (For detailed review of the evidence, please refer to section 6.2.2.3 of [FDA Review Memorandum Dated April 18, 2023](#))
- Immunogenicity of a Single Booster Dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) 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 in Individuals 5 through 11 Years of Age (section 6.2.2.3 of [FDA Review Memorandum Dated April 18, 2023](#))
- Effectiveness of Additional Doses Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in Immunocompromised Individuals (For detailed review of the evidence, please refer to section 6.5 of [FDA Review Memorandum Dated April 18, 2023](#))

### **6.1.3 Conclusion**

The effectiveness data accrued with the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) (no longer authorized for use in the U.S.) and Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are relevant to Pfizer-BioNTech Vaccine (2023-2024 Formula) because these vaccines are manufactured using the same process. The effectiveness of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is based on totality of the evidence from clinical trials, including efficacy and effectiveness data of the Pfizer-BioNTech COVID-19

Vaccine (Original monovalent) and immunogenicity data of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). It is reasonable to expect, from extrapolation of immunogenicity in individuals 5 years of age and older and from inference of efficacy and immunogenicity in individuals 6 months through 4 years of age, that Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula) may be effective in individuals 6 months through 11 years of age. In addition, preclinical data demonstrate that, when compared with the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) induces higher neutralizing antibody titers against XBB sublineages, including XBB.1.5, XBB.1.16, XBB.1.16.1, and XBB.2.3.

Consequently, to address the urgent public health need for COVID-19 vaccine more closely matched to circulating variants, FDA considers it appropriate to issue an EUA for the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) based on relevant safety and effectiveness evidence from previously authorized and currently authorized or approved Pfizer-BioNTech COVID-19 vaccines manufactured using the same process in addition to supportive pre-clinical animal data for the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula).

## 6.2 Safety Data

Please refer to [prior FDA review memoranda](#) for detailed review of the safety data from clinical studies that supported authorization of Pfizer-BioNTech COVID-19 vaccines.

The safety of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) in individuals 6 months of age through 11 years of age is based on the following evidence:

- Safety data from clinical studies which evaluated primary and booster vaccination with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). Please refer to section 6 of [EUA Memorandum Dated May 17, 2022](#) for detailed review. Safety data pertaining to additional safety follow up were also reviewed in support of this EUA. For detailed review of this follow-up data, please refer to the clinical memorandum supporting the approval of STN 125742/276.
- Safety data from clinical studies that evaluated booster vaccination with Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Please refer to section 6 of the [EUA memorandum dated March 14, 2023](#) for detailed review.
- Safety data from a clinical study which evaluated a booster dose of bivalent vaccine (Original and Omicron BA.1). Please refer to section 6 of the [EUA memorandum dated August 31, 2022](#) for detailed review.

The safety data accrued with the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are relevant to Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula) because all these vaccines are manufactured using the same process.

A high-level summary of postmarketing safety data is provided below.

### 6.2.1 Postmarketing Safety

Review of postmarketing safety data indicate a similar safety profile of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Although the most current worldwide and U.S. administration data are not known, estimated distribution data may serve as an indicator of vaccine exposure. Per Pfizer's Abbreviated Summary Monthly Safety Report (dated July 13, 2023), as of June 18,

2023, approximately (b) (4) doses of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and (b) (4) doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) have been shipped worldwide since respective vaccine authorization dates. Per last CDC administration data on May 11, 2023, more than 366 million doses of the original Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) have been administered in the U.S., and 36,730,941 doses of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). Of the total doses of either the Original or Bivalent formulation given in the U.S., more than 3 million have been administered to individuals 6 months through 4 years of age and more than 22 million have been administered to individuals 5 through 11 years of age.

In recipients of all doses of Pfizer-BioNTech COVID-19 vaccines (Original and Bivalent) among children less 6 months to less than 12 years of age, most frequently reported preferred terms (PTs) reported to the Vaccine Adverse Event Reporting System (VAERS) were incorrect dose administered, product preparation issue, expired product administered, product administered to patient of inappropriate age, product storage error, pyrexia, incorrect product formulation administered, vomiting, headache, and fatigue. The Sponsor is conducting additional safety-related post-authorization/postmarketing studies for the Pfizer-BioNTech COVID-19 Vaccine, including postmarketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. The Sponsor is also conducting post-authorization studies to evaluate the association between the Pfizer-BioNTech COVID-19 Vaccine and a pre-specified list of adverse events of special interest (AESIs) in all authorized ages in the general U.S. population (refer to section 7 for details).

Taken together, these data informed FDA's assessment of the known and potential benefits and risks of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula). Based upon the accumulated experience with all doses of Pfizer-BioNTech COVID-19 vaccines to date, FDA determined that it was reasonable to extrapolate the available safety data, supporting a favorable benefit-risk profile for use of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024) and the proposed updated vaccination schedule.

## **7 FDA Review of Other Information Submitted in Support of the EUA Amendment**

### **7.1 Chemistry Manufacturing and Control (CMC) Information**

Similar to the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) (Omicron XBB.1.5) is a nucleoside-modified messenger RNA (modRNA)-based COVID-19 vaccine encoding the full-length spike (S) glycoprotein of SARS-CoV-2 Omicron XBB.1.5 sublineage and is formulated with lipids ALC-0315, ALC-0159, DSPC, and cholesterol to form lipid nanoparticles (LNPs). Compared with Comirnaty Original, monovalent, the major changes made to the XBB.1.5 vaccine are limited to the strain-specific modifications in the S-protein sequence, including (b) (4) amino acid substitutions and (b) (4) amino acid deletions. Based on the extensive manufacturing experience with other Pfizer-BioNTech COVID-19 vaccines based on SARS-CoV-2 variants (e.g., Alpha, Beta, Delta, Omicron BA.1, and Omicron BA.4/BA.5), these changes in sequence are not expected to impact the physicochemical properties, processability, quality, and stability of the XBB.1.5 mRNA drug substance (DS) and the resulting LNP drug product (DP). Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is manufactured based on the licensed/authorized BNT162b2 vaccine platform with equivalent manufacturing processes, control strategies, and quality attributes being implemented for the linear DNA template (as a starting material), mRNA DS, and LNP DP.

(b) (4) large-scale confirmatory Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) DS (b) (4) was manufactured at one of the previously approved manufacturing sites (Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC, 1 Burt Road, Andover MA 01810 (FEI: 1222181)). The final release data of this DS (b) (4) confirmed the use of BNT162b2 platform manufacturing process for the production of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) DS with comparable quality as the licensed Comirnaty vaccine.

Similar to the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) that would be supplied under the EUA is formulated in Tris/Sucrose buffer at two mRNA concentration levels, 0.1 mg/mL and 0.033 mg/mL, and filled in glass vials as multi-dose vial (MDV) or single-dose vial (SDV) presentations.

For the 10-µg mRNA dose of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) for use in individuals 5 through 11 years of age, the following three DP presentations are reviewed as a part of the CMC submission:

- 0.1 mg/mL dilute-to-use MDV filled at 1.3 mL fill volume, providing a total of 10 doses after dilution with 1.3 mL saline, with each dose in a 0.2 mL injection volume (this presentation is not part of the authorization being considered for the September 11, 2023, action on EUA 27034)
- 0.033 mg/mL ready-to-use MDV filled at 2.25 mL fill volume, providing a total of 6 doses per vial, with each dose in a 0.3 mL injection volume (this presentation is not part of the authorization being considered for the September 11, 2023, action on EUA 27034). No dilution is needed.
- 0.033 mg/mL ready-to-use SDV filled at 0.48 mL fill volume with a dose of 0.3 mL. No dilution is needed.

For the 2023-2024 Formula, only the 0.033 mg/mL ready-to-use SDV presentation for the 10-µg mRNA dose is planned for launch in the U.S. Other than the 10-µg Omicron XBB.1.5-encoding mRNA, each 0.3 mL dose of this vaccine presentation also includes the following ingredients: lipids (0.14 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.02 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.03 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.06 mg cholesterol), 31 mg sucrose, 0.06 mg tromethamine, and 0.4 mg tromethamine hydrochloride.

For the 3-µg mRNA dose of the Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula) for use in individuals 6 months to < 5 years of age, the following two DP presentations are introduced:

- 0.1 mg/mL dilute-to-use MDV filled at 0.4 mL fill volume, providing a total of 10 doses after dilution with 2.2 mL saline, with each dose in a 0.2 mL injection volume (this presentation is not part of the authorization being considered for the September 11, 2023, action on EUA 27034).
- 0.033 mg/mL dilute-to-use MDV filled at 0.48 mL fill volume, providing a total of 3 doses after dilution with 1.1 mL saline, with each dose in a 0.3 mL injection volume.

For the 2023-2024 Formula, only the 0.033 mg/mL 3-dose dilute-to-use MDV presentation for the 3-µg mRNA dose is planned for launch in the U.S. Other than the 3-µg Omicron XBB.1.5-

encoding mRNA, each 0.3 mL dose of this vaccine presentation also includes the following ingredients: lipids (0.04 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.005 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.01 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.02 mg cholesterol), 9.4 mg sucrose, 0.02 mg tromethamine, and 0.12 mg tromethamine hydrochloride. In addition, the diluent (sterile 0.9% Sodium Chloride Injection, USP) contributes 1.88 mg sodium chloride per dose.

Three large-scale confirmatory Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) DP lots, including one 10-µg (0.1 mg/mL) dilute-to-use MDV, one 10-µg (0.033 mg/mL) ready-to-use SDV, and one 10-dose 3-µg (0.1 mg/mL) dilute-to-use MDV, were manufactured at Pfizer Puurs, one of the previously approved DP manufacturing facilities. The lot release results from these three DP lots demonstrated that consistent manufacturing of the BNT162b2 variant vaccines can be achieved with a well-established mRNA vaccine platform. Using a (b) (4) strategy, data obtained from the 10-µg ready-to-use SDV also support authorization of the 10-µg ready-to-use MDV and 3-dose 3-µg dilute-to-use MDV.

The specifications for the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) DS and DP are based on those established for the licensed Comirnaty vaccine, with only modifications made to the identity testing of mRNA sequence in XBB.1.5 (b) (4) DP. Using XBB.1.5-specific primers/probes, specificity of the identity test methods (b) (4) was demonstrated, supporting their intended use for distinguishing XBB.1.5 mRNA sequence from that of the original vaccine and other Omicron variants. Though no changes are made to the (b) (4) analytical procedure, a supplemental validation study was conducted, and based on evaluations on assay specificity and detection limit, the (b) (4) assay is concluded to be suitable for its intended use to confirm the (b) (4) of XBB.1.5 mRNA.

The initial shelf life of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is set to be 18 months for the 0.1 mg/mL DP and 12 months for the 0.033 mg/mL DP when stored frozen at -90 to -60°C in vials. These shelf lives are based on real-time stability data generated from the corresponding 0.1 mg/mL and 0.033 mg/mL Pfizer-BioNTech COVID-19 Vaccines (Original monovalent). The available stability data from the original vaccines also support an allowance for short-term storage at 2° to 8°C for up to 10 weeks at the point of use, counted within the corresponding 18- or 12-month shelf life.

## 7.2 Facilities

The manufacture of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) is performed at existing facilities that were previously included in the EUA for the manufacture of the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). These facilities are currently included in the EUA for the manufacture of the authorized 3 µg/dose and 10 µg/dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). No changes were made to the facilities, equipment, container closure systems, quality systems and controls. FDA finds that all facilities within the scope of this authorization for the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) are adequate to support its use under an EUA.

## 7.3 Nonclinical Studies

Immunogenicity of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) has been evaluated in mice. The vaccine was tested in both naïve mice as a two-dose primary series and BNT162b2 vaccine-experienced mice as a fourth dose. When compared with the bivalent (Original and Omicron BA.4/BA.5) vaccine, both the XBB.1.5-modified monovalent and bivalent (1:1 mixture of Omicron XBB.1.5 and BA.4/BA.5) vaccines induced higher neutralizing antibody

titers against XBB sublineages, including XBB.1.5, XBB.1.16, XBB.1.16.1, and XBB.2.3. The strongest immune responses against XBB sublineages were observed in monovalent XBB.1.5 vaccine-immunized mice. In addition, all Omicron sublineage-modified vaccines induced comparable T-cell responses with a Th1-dominant profile, which is consistent with prior nonclinical data for the Pfizer-BioNTech COVID-19 Vaccine (Original monovalent). These data are therefore considered supportive for the strain change to Omicron XBB.1.5 sublineage for the Pfizer-BioNTech COVID-19 Vaccine (2023-2024).

#### **7.4 Pharmacovigilance Activities**

Pfizer is conducting safety-related post-authorization/postmarketing studies for Pfizer-BioNTech COVID-19 vaccines, including postmarketing requirements to assess known serious risks of myocarditis and pericarditis and an unexpected serious risk of subclinical myocarditis. Pfizer has a pharmacovigilance plan to monitor safety concerns that could be associated with the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula). The plan includes the following safety concerns:

- Important Identified Risks: anaphylaxis, myocarditis, and pericarditis
- Important Potential Risks: None.
- Missing information: Use in Pregnancy, vaccine effectiveness, use in pediatric individuals <6 months of age.

The previous important potential risk VAED/VAERD was removed from the list of safety concerns because the available cumulative safety data (clinical trial and postmarketing data) has not substantiated retaining VAED/VAERD as an important potential risk. VAED/VAERD will continue to be monitored through routine pharmacovigilance.

##### **7.4.1 Sponsor Pharmacovigilance Activities**

The Sponsor will conduct passive and active surveillance to monitor the post-authorization safety for the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), 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). 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 associated with an AE; and newly identified safety concerns. The EUA Letter of Authorization will be revised from a required monthly submission of periodic safety reports to require such reports “monthly or at another appropriate reporting interval determined by the Office of Biostatistics and Pharmacovigilance.” This change will provide flexibility to modify the reporting interval in the future, if appropriate, given the extensive global safety data base and the continued accumulation of postmarketing safety data on the Pfizer-BioNTech COVID-19 vaccines.”
- Post-authorization observational studies to evaluate the association between the Pfizer-BioNTech COVID-19 Vaccine 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. These studies are being 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 (2023-2024 Formula) in children less than 12 years of age in the following safety studies:

- **C4591008** - HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 Vaccine in U.S. healthcare workers, their families, and their communities.  
Objective: To characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease, among individuals vaccinated with the BNT162b2 since EUA.
- **C4591009** - A non-interventional post-approval safety study of the Pfizer-BioNTech COVID-19 vaccine in the U.S.  
Objective: To assess the occurrence of safety events of interest, including myocarditis, among individuals in the general U.S. population of all ages, and in subcohorts of interest within selected data sources participating in the U.S. Sentinel System.
- **C4591011** - Active safety surveillance of the Pfizer-BioNTech COVID-19 Vaccine in the U.S. Department of Defense population following Emergency Use Authorization.  
Objective: To assess whether individuals in the U.S. DoD Military Health System (MHS) experience increased risk of safety events of interest, following receipt of the COVID-19 mRNA Vaccine.
- **C4591012** - Post-emergency use authorization active safety surveillance study among individuals in the Veteran's Affairs Health System receiving Pfizer-BioNTech 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, following receipt of the COVID-19 mRNA vaccine, including the Bivalent Omicron-modified vaccine.
- **C4591021** - Post-conditional approval active surveillance study among individuals in Europe receiving the Pfizer-BioNTech Coronavirus Disease (COVID-19) vaccine.  
Objective: To assess the potential increased risk of adverse events of special interest (AESI), after being vaccinated with COVID-19 mRNA vaccine, in all authorized age groups, including individuals less than 12 years of age.
- **C4591036** - Pediatric Heart Network 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.
- **C4591038** - (former, C4591021 sub study): post-authorization active surveillance study of myocarditis and pericarditis among individuals in Europe receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) vaccine.  
Objective: To describe the clinical course (treatment, survival, hospitalization, long-term cardiac outcome) of myocarditis and pericarditis among individuals diagnosed with myocarditis and/or pericarditis after receiving at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination, using a cohort study design.
- **C4591049** - HERO-Together Boost: A post-Emergency Use Authorization (EUA) observational cohort study to evaluate the safety of the Pfizer-BioNTech Bivalent Coronavirus Disease 2019 (COVID-19) vaccine.

Objective: To characterize the real-world incidence of safety events of interest, including events indicative of severe or atypical COVID-19 disease, among individuals vaccinated with the Bivalent Omicron-modified vaccine, since EUA.

- **C4591051** - A non-interventional post-approval safety study of Pfizer-BioNTech COVID-19 vaccine in the U.S.

Objective: To assess the occurrence of safety events of interest following receipt of the COVID-19 bivalent Omicron-modified vaccine in the general U.S. population of all ages.

- **C4591052** - Post-Authorization Safety Study of Comirnaty Original/Omicron BA.1 and Comirnaty Original/Omicron BA.4-5 in Europe.

Objective: To assess the potential increased risk of adverse events of special interest (AESI), including myocarditis/pericarditis, after being vaccinated with COVID-19 bivalent Omicron-modified vaccine, in all authorized age groups.

- **C4591062** - Post approval Observational Cohort Study to Evaluate the Safety of the COMIRNATY 2023-2024 Formula in the U.S.

Objective: To evaluate safety of the COMIRNATY (2023-2024 Formula) in all authorized and/or approved age groups.

Additionally, the Sponsor is conducting the following effectiveness study:

- **C4591014** - Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study – Kaiser Permanente Southern California.

Objective: To estimate the effectiveness of COVID-19 mRNA vaccine against hospitalization and emergency department admission for acute respiratory illness due to SARS-CoV-2 infection and to assess the effectiveness of Bivalent Omicron-modified vaccines and the 2023-2024 Formula-modified vaccine following their introduction, in all authorized age groups.

#### **7.4.2 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
- Cases of COVID-19 that result in hospitalization or death

Additionally, potential vaccination errors are mitigated through coloration of the vial caps and borders, information in the label, and available education materials for Healthcare Providers.

#### **7.5 EUA Prescribing Information and Fact Sheets**

The Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), and 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 (2023-2024 Formula) in Individuals 6 Months of Age and Older**

### **8.1 Discussion of Benefits, Risks, and Uncertainties**

COVID-19 is caused by SARS-CoV-2 and the virus has been responsible for over 104 million cases of COVID-19 and over 1.1 million deaths in the U.S. Since the start of the pandemic, there has been a succession of SARS-CoV-2 variants, including Beta, Delta, Omicron BA.1, and most recently Omicron BA.5, BQ.1.1, XBB.1.5, and other Omicron sublineages. Current treatment options for COVID-19 include antiviral medications, immune modulators, and convalescent plasma. These interventions are generally most effective in diseases of mild to moderate severity. Although treatments exist for those infected with SARS-CoV-2, they are usually not effective for individuals with 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 may 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. Currently authorized COVID-19 vaccines for disease prevention in individuals 6 months of age and older include the mRNA-based vaccines from Moderna and Pfizer-BioNTech, and an adjuvanted, protein subunit vaccine from Novavax (in individuals 12 years of age and older only).

The original monovalent COVID-19 vaccines were 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. Vaccine effectiveness against symptomatic disease declined more rapidly than that against serious disease, as illustrated by studies conducted in the U.S.,<sup>23,24</sup> Israel,<sup>25</sup> Qatar,<sup>26</sup> Portugal,<sup>27</sup> Israel,<sup>25</sup> Qatar,<sup>26</sup> Portugal,<sup>27</sup> and England.<sup>28</sup> In the setting of the viral variants that have emerged in the past, booster doses with available vaccines (based on the ancestral strain) were able to restore some degree of protection against serious and symptomatic disease.

The immunogenicity and safety of mRNA booster vaccines developed against the Beta, Delta, and Omicron BA.1 variants have been evaluated previously by both Moderna and Pfizer-BioNTech. However, these booster vaccines were not deployed in the U.S. due to the rapid evolution of the SARS-CoV-2 variants. Following emergence of the Omicron variant and its sublineages (BA.4/BA.5 and related sublineages) in November 2021, and based on data suggesting improved protection against Omicron sublineages conferred by the bivalent vaccines [Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5); Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)] compared to the original monovalent [Pfizer-BioNTech COVID-19 Vaccine (Original monovalent), Moderna COVID-19 Vaccine (Original monovalent)] COVID-19 vaccines, FDA, on August 31, 2022, authorized use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for booster doses in individuals 12 or 18 years of age and older, respectively. In April 2023, the FDA authorized the use of the bivalent COVID-19 vaccines for all doses in individuals 6 months of age and older allowing for use of a single dose in most adults and pediatric populations; two or three doses (based on the vaccine used) in the youngest pediatric populations; an additional dose for persons 65 years of age and older; and additional age-appropriate doses for persons with

certain kinds of immunocompromise. The EUA actions on April 18, 2023, resulted in FDA no longer authorizing use of original monovalent COVID-19 Moderna and Pfizer-BioNTech COVID-19 vaccines (containing the mRNA encoding spike protein of Original SARS-CoV-2 virus) in the U.S. and no longer authorizing certain uses of the approved COVID-19 vaccines in the U.S.

Bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines provided improved protection from COVID-19 caused by sublineages of Omicron including the BA.4/BA.5 sublineages compared with the original monovalent COVID-19 vaccines. However, the effectiveness of bivalent (Original and Omicron BA.4/BA.5) COVID-19 vaccines against Omicron sublineages, including the most recently circulating sublineages, appears to wane over time (refer to section [3.1](#)), suggesting that an updated strain composition of COVID-19 vaccines to more closely match currently circulating Omicron sublineages is warranted.

The safety and effectiveness data accrued with Pfizer-BioNTech COVID-19 Vaccine, Bivalent are relevant to Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), because these vaccines are manufactured using the same process. Nonclinical data reviewed with XBB.1.15 indicated that Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) when administered to vaccine naïve or vaccine experienced laboratory animals, elicited higher neutralizing antibodies compared to the bivalent vaccine (Original and Omicron BA.4/BA.5) against currently circulating XBB-related sublineages. Based on the totality of the available evidence (reviewed in detail in sections [6](#) and [7](#)), it is reasonable to expect in immunocompetent and immunocompromised individuals 6 months through 11 years of age that the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) will likely increase immune responses and clinical protection against SARS-CoV-2 variants, including the currently predominant Omicron sublineages, compared to Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

Additional 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 FDA Biologics Effectiveness and Safety (BEST) System, within a week after second dose of mRNA-based COVID-19 vaccine primary series, the crude observed rate (without adjustment for delay of reporting and other factors) of myocarditis or pericarditis events was 2.1 per 100,000 doses for individuals aged 18–64 years (unpublished data), and 12.5 per 100,000 doses for males aged 18–25 years.<sup>28</sup> Within a week after a second dose of vaccine, the adjusted observed rate of myocarditis or pericarditis for individuals aged 18–64 years who received mRNA-based COVID-19 vaccines was 1.8 per 100,000 doses (unpublished data), and 13.0 per 100,000 doses for males aged 18–25 years. The meta-analysis of BEST data for the Pfizer COVID-19 Vaccine reports excess cases per one million second doses for 12–15-year-old males as 132.2 (95%CI: 92.0-189.6), for 16-17-year-old males as 159.9 (95%CI: 59.9- 414.3), and for 18-25-year-old males as 95.6 (95%CI: 61.0-147.4). Based on the data from BEST, within a week after the second dose of the 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 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 new safety concerns in addition to those previously characterized. In addition, passive and active surveillance systems will be used to continuously monitor adverse reactions and any emerging safety concerns post EUA.

Clinical evaluation of bivalent mRNA COVID-19 vaccines has not suggested new safety concerns additional to the extensively characterized safety profile of originally authorized and approved mRNA COVID-19 vaccines. Post-deployment monitoring for adverse events using both passive and active surveillance systems will be used to assess whether any new safety concerns emerge. [Table 3](#) provides a summary of the benefit-risk considerations in a standard FDA format.

**Table 3. Summary of Benefit-Risk Assessment**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>• COVID-19 caused by SARS-CoV-2 has been responsible for nearly 104 million cases and 1.1 million deaths in the U.S.</li> <li>• There has been a succession of variants (Delta, Omicron BA.1, BA.5, and more recently XBB.1.5, among others) that have led to a reduction in vaccine effectiveness.</li> <li>• Although the available bivalent COVID-19 vaccines continue to provide some protection against hospitalization and death, their overall effectiveness appears to have decreased.</li> </ul>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Original monovalent mRNA-based COVID-19 vaccines authorized in the U.S. initially had high effectiveness (90-95%) against symptomatic disease; however, in combination with waning individual immunity, vaccine effectiveness declined with the emergence of the now dominant Omicron variant; this effect is most prominently observed in older individuals; decreased vaccine effectiveness, especially after the primary series, is also apparent in pediatric age groups.</li> </ul>
<b>Current Options for Treatment or Prevention of COVID-19 Disease</b>	<ul style="list-style-type: none"> <li>• Antiviral medications, immune modulators, and convalescent plasma have been approved or authorized for the management of individuals with COVID-19; they are generally most effective in disease of mild to moderate severity.</li> <li>• Currently, there are two authorized bivalent mRNA COVID-19 vaccines for use in the U.S. as a two or three dose series in 6 months through 4 or 5 years of age and as a single dose in 5 or 6 years of age and older.</li> <li>• An adjuvanted, protein subunit COVID-19 vaccine is authorized for use as a primary series in individuals 12 years of age and older and as a single booster dose for certain individuals 18 years of age and older.</li> </ul>	<ul style="list-style-type: none"> <li>• 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)</li> <li>• COVID-19 vaccination has been a cornerstone of the pandemic response, as vaccines may provide protection against COVID-19.</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Benefit</b>	<ul style="list-style-type: none"> <li>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.</li> <li>Preclinical data demonstrating that Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula), when used in vaccine naïve or vaccine experienced laboratory animals, elicited higher neutralizing antibodies compared to the bivalent vaccine (Original and Omicron BA.4/BA.5) against circulating XBB-related sublineages.</li> <li>Residual uncertainty remains in how the magnitude of the expected increase in antibody response in humans will translate into effectiveness against COVID-19 outcomes, including symptomatic and serious disease</li> </ul>	<ul style="list-style-type: none"> <li>The totality of the available evidence indicates that Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula) may provide benefit, particularly against circulating XBB sublineages.</li> <li>Given the enhanced neutralizing antibody activity against more recently circulating SARS-CoV-2 variants demonstrated in nonclinical studies of Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula) compared with the current bivalent (Original and Omicron BA.4/BA.5), it is reasonable to expect that administration of Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula) doses may provide additional benefit compared with administration of Pfizer BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).</li> </ul>

**8.2 Conclusions Regarding Benefit-Risk**

For individuals 6 months through 11 years of age, the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) outweigh the known and potential risks of the vaccine, when used as described in Section 5.1 for all doses appropriate to age and immunocompromise, 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 in part on real-world evidence that clearly demonstrated the benefits of available COVID-19 vaccines, concluded that benefits outweighed risks (please refer to section 8 of [FDA Review Memorandum Dated April 18, 2023](#)). During the current wave of COVID-19 caused in large part by the XBB-related sublineages, administration of a Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula) is expected to have a favorable benefit-risk profile and to restore protection against serious outcomes from COVID-19.

**9 Overall Summary and Recommendations**

Following review of the EUA request, and VRBPAC recommendations from the June 15, 2023, meeting, the review team considered the following in its assessment of the Pfizer-BioNTech Vaccine (2023-2024 Formula):

- 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 includes the following:

- Preclinical data demonstrating that Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula) when administered to vaccine naïve or vaccine experienced laboratory animals, elicited higher neutralizing antibodies compared to the bivalent vaccine (Original and Omicron BA.4/BA.5) against XBB-related sublineages,
  - Chemistry, Manufacturing and Control Information related to single-dose and multi-dose vial presentations of Pfizer BioNTech COVID-19 Vaccine, (2023-2024 Formula) including the manufacturing facilities,
  - Clinical safety, immunogenicity, efficacy, and observational effectiveness data from studies which evaluated primary and booster vaccination with the Pfizer BioNTech COVID-19 Vaccine (Original monovalent) and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5),
  - Postmarketing safety surveillance data of the original Pfizer-BioNTech COVID-19 Vaccine and the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) and,
  - Literature evidence, including population-based seroprevalence and COVID-19 incidence rates, along with data from real world studies.
- Although available evidence suggests that the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) continues to provide protection against serious disease from COVID-19 in the U.S., based on the totality of available scientific evidence, it is reasonable to conclude that the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), administered as a single dose to all immunocompetent individuals (unvaccinated or vaccinated) 5 through 11 years of age at least 2 months following any prior original monovalent or bivalent COVID-19 vaccine dose, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages.
  - Based on the totality of available scientific evidence, in previously unvaccinated immunocompetent individuals 6 months through 4 years of age, it is reasonable to conclude that the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) administered as three doses may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages.
  - Based on the totality of available scientific evidence, in immunocompetent individuals 6 months through 4 years of age who have already received one dose of Pfizer-BioNTech COVID-19 Vaccine or Pfizer BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), it is reasonable to conclude that the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), administered as two doses, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages.
  - Based on the totality of available scientific evidence, in immunocompetent individuals 6 months through 4 years of age who have already received two to four doses of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or Pfizer BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), it is reasonable to conclude that the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula), administered as a single dose, may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages.

- Based on the totality of available scientific evidence, it is reasonable to conclude that administration of age-appropriate dose(s) of Pfizer BioNTech COVID-19 Vaccine (2023-2024 Formula) in individuals with certain kinds of immunocompromise 6 months through 11 years of age may be effective in preventing serious or life-threatening disease or conditions that can be caused by SARS-CoV-2, including XBB-related sublineages, as noted below:
  - a three-dose series in unvaccinated immunocompromised individuals
  - one or two dose(s) administered as appropriate to complete the three-dose series in immunocompromised individuals previously vaccinated with Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) and/or the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)
  - a single dose administered at least 2 months after the last previous dose of Pfizer-BioNTech COVID-19 Vaccine (Original monovalent) or Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in previously vaccinated immunocompromised individuals 6 months through 4 years of age, who have received three or more doses
  - a single dose administered at least 2 months following the last previous dose of a COVID-19 vaccine (Original monovalent) or a bivalent COVID-19 vaccine in previously vaccinated immunocompromised individuals 5 through 11 years of age, who have received three or more doses
  - an additional dose of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) in immunocompromised individuals 6 months through 4 years of age at least 2 months following the last dose of a Pfizer-BioNTech COVID-19 vaccine (2023-2024 Formula) in at least a three-dose series in which at least 1 dose was with Pfizer-BioNTech COVID-19 vaccine (2023-2024 Formula)
  - an additional dose of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) in immunocompromised individuals 5 through 11 years of age at least 2 months following the last dose of a COVID-19 vaccine (2023-2024 Formula) in at least a three-dose series in which at least 1 dose was with Pfizer-BioNTech COVID-19 vaccine (2023-2024 Formula) or Moderna COVID-19 vaccine (2023-2024 Formula)
  - age-appropriate additional doses of Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances, with the timing of the additional doses based on the individual's clinical circumstances
- As summarized in section [6](#), effectiveness of the Pfizer-BioNTech COVID-19 Vaccine, (2023-2024 Formula) is supported by a combination of clinical studies and real-world evidence.
- 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, (2023-2024 Formula) outweigh the known and potential risks when used appropriate to age and immune status for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months through 11 years of age.
- Known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) include reduction in the risk of symptomatic COVID-19 and associated serious sequelae, including from COVID-19 due to XBB-related sublineages.

- Uncertainties include those around the level of effectiveness against future SARS-CoV-2 variants, effectiveness against asymptomatic SARS-CoV-2 infection and SARS-CoV-2 transmission, especially in children, 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, and axillary swelling/tenderness) and rarely anaphylaxis and myocarditis/pericarditis based on experience in original Pfizer-BioNTech COVID-19 Vaccine recipients. Risks that should be further evaluated include quantifying the rate of vaccine-associated myocarditis/pericarditis and surveillance for other adverse reactions that may become apparent with widespread use of the vaccine and with longer duration of follow-up.

Based on the considerations outlined above, the review team recommends: 1) removing authorization for emergency use of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) in the U.S.; and 2) revision of the EUA to provide for use of the Pfizer-BioNTech COVID-19 (2023-2024 Formula) administered in an appropriate schedule based on age and immune status, as reflected in the Fact Sheets.

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## 11 Appendices

### Appendix A. Adverse Events of Special Interest

Body System/Classification Adverse Event of Special Interest	Estimated Risk Window (Days)
Autoimmune diseases	--
Guillain-Barré syndrome <sup>1</sup>	1-42
Acute disseminated encephalomyelitis	1-42
Narcolepsy <sup>1</sup>	1-42 <sup>2</sup>
Acute aseptic arthritis	1-42 <sup>4</sup>
Diabetes (type 1 and broader)	Any
(Idiopathic) thrombocytopenia <sup>1</sup>	1-42
Heparin-induced thrombocytopenia (HIT)-like event <sup>1</sup>	1-15
Cardiovascular system	--
Acute cardiovascular injury including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia	Any <sup>5</sup>
Myocarditis <sup>1</sup> , Pericarditis <sup>1</sup> , Myocarditis and pericarditis <sup>1</sup>	1-14 after each dose 1-7 after each dose
Circulatory system	--
Coagulation disorders: thromboembolism, hemorrhage	1-28
Single organ cutaneous vasculitis	1-286
Hepato- gastrointestinal and renal system	--
Acute liver injury	1-42 <sup>8</sup>
Acute kidney injury	1-42 <sup>8</sup>
Acute pancreatitis	1-42 <sup>8</sup>
Rhabdomyolysis	Any
Nerves and central nervous system	--
Generalized convulsion	1-42
Meningoencephalitis	1-42
Transverse myelitis <sup>1</sup>	1-42
Bell's palsy	1-42
Respiratory system	--
Acute respiratory distress syndrome	Any
Skin and mucous membrane, bone and joints system	--
Erythema multiforme	1-42 <sup>7</sup>
Chilblain-like lesions	1-42 <sup>6</sup>
Other system	
Anosmia, ageusia	1-42
Anaphylaxis <sup>1</sup>	1
Multisystem inflammatory syndrome	1-42 <sup>3</sup>
Death (any causes)	Any
Subacute thyroiditis	1-42 <sup>4</sup>
Sudden death	Any
Gestational diabetes	Any time pregnancy
Pregnancy outcome, maternal	--
Preeclampsia	Any time pregnancy
Maternal death	Any time pregnancy
Fetal growth restriction	Any time pregnancy

<b>Body System/Classification Adverse Event of Special Interest</b>	<b>Estimated Risk Window (Days)</b>
Pregnancy outcome, neonates. Define design taking trimester into account	--
Spontaneous abortions	After vaccination
Stillbirth	After vaccination
Preterm birth	At preterm birth
Major congenital anomalies <sup>a</sup>	1 year after birth
Microcephaly	At birth
Neonatal death	At birth
Termination of pregnancy for fetal anomaly	At termination
COVID-19 Disease	Any
Any	--
Vaccine-associated enhanced disease (VAED) <sup>1</sup>	Any

Source: Sponsors Clinical Study Protocol C4591021

1. For this AESI clinical validation will occur.

2. Published risk and control intervals for demyelinating diseases and cranial disorders were applied to TM and narcolepsy/cataplexy.

3. As severe COVID-19 ranges from severe pneumonia, acute respiratory distress syndrome, and multisystem organ failure/MIS-A, a 1 to 42 day risk interval was applied in order to capture the 14-day incubation period of the disease and 4-5 day period from exposure to symptom onset.

4. Published risk and control intervals for autoimmune disorders were applied to similar autoimmune rheumatic conditions (i.e., fibromyalgia and autoimmune thyroiditis).

5. Published risk and control intervals for myocarditis and pericarditis were applied to other cardiovascular conditions (i.e., heart failure and cardiogenic shock, stress cardiomyopathy, coronary artery disease, arrhythmia, acute myocardial infarction).

6. Similar risk and control intervals were applied to all cardiovascular and hematological disorders characterized by damage to the blood vessels and/or arteries and clotting (i.e., microangiopathy, deep venous thrombosis, pulmonary embolus, limb ischemia, hemorrhagic disease, disseminated intravascular coagulation, chilblain-like lesions). The published risk and control intervals for KD were applied to vasculitides given that KD is a type of medium and small-vessel vasculitis.

7. Published risk and control intervals for non-anaphylactic allergic reactions were applied to hypersensitivity disorders (i.e., erythema multiforme).

8. Risk intervals of 42 days were applied for acute kidney injury and liver injury to be consistent with other COVID-19 related safety events of interest.

## Appendix B. List of Preferred Terms Used in the Enhanced Analysis for Potential Cases of Myocarditis or Pericarditis, Based on CDC Case Definition

The following PTs were used in the enhanced analysis to identify potential cases of myocarditis or pericarditis based on the CDC case definition.

- acute chest syndrome
- angina pectoris
- autoimmune myocarditis
- autoimmune pericarditis
- cardiac dysfunction
- cardiac function test abnormal
- cardiomyopathy
- cardiovascular function test abnormal
- chest discomfort
- chest pain
- conduction disorder
- defect conduction intraventricular
- dyspnea
- dyspnea at rest
- dyspnea exertional
- ECG electrically inactive area
- ECG P wave inverted
- ECG signs of myocardial infarction
- ECG signs of myocardial ischemia
- ECG signs of ventricular hypertrophy
- electrocardiogram abnormal
- electrocardiogram ST segment
- electrocardiogram ST segment abnormal
- electrocardiogram ST segment depression
- electrocardiogram ST segment elevation
- electrocardiogram ST-T segment depression
- electrocardiogram ST-T segment abnormal
- electrocardiogram ST-T segment elevation
- eosinophilic myocarditis
- giant cell myocarditis
- hypersensitivity myocarditis
- immune-mediated myocarditis
- magnetic resonance imaging heart
- musculoskeletal chest pain
- myocardial edema
- myocarditis
- painful respiration
- palpitations
- pericardial effusion
- pericardial effusion malignant
- pericardial rub
- pericarditis
- pericarditis constructive
- pleuropericarditis
- syncope
- troponin
- troponin C
- troponin I
- troponin I increased
- troponin I normal
- troponin T increased

**Appendix C4. CDC Working Case Definitions of Probable and Confirmed Myocarditis, Pericarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines**

Condition	Probable Case Definition	Confirmed Case Definition
<b>Acute myocarditis</b>	<p>Presence of <math>\geq 1</math> new or worsening of the following clinical symptoms:<sup>a</sup></p> <ul style="list-style-type: none"> <li>• chest pain, pressure, or discomfort</li> <li>• dyspnea, shortness of breath, or pain with breathing</li> <li>• palpitations</li> <li>• syncope</li> </ul> <p><b>OR</b>, infants and children aged &lt;12 years might instead have <math>\geq 2</math> of the following symptoms:</p> <ul style="list-style-type: none"> <li>• irritability</li> <li>• vomiting</li> <li>• poor feeding</li> <li>• tachypnea</li> <li>• lethargy</li> </ul> <p><b>AND</b></p> <p><math>\geq 1</math> new finding of</p> <ul style="list-style-type: none"> <li>• troponin level above upper limit of normal (any type of troponin)</li> <li>• abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis<sup>c</sup></li> <li>• abnormal cardiac function or wall motion abnormalities on echocardiogram</li> <li>• cMRI findings consistent with myocarditis<sup>c</sup></li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• No other identifiable cause of the symptoms and findings</li> </ul>	<p>Presence of <math>\geq 1</math> new or worsening of the following clinical symptoms:<sup>a</sup></p> <ul style="list-style-type: none"> <li>• chest pain, pressure, or discomfort</li> <li>• dyspnea, shortness of breath, or pain with breathing</li> <li>• palpitations</li> <li>• syncope</li> </ul> <p><b>OR</b>, infants and children aged &lt;12 years might instead have <math>\geq 2</math> of the following symptoms:</p> <ul style="list-style-type: none"> <li>• irritability</li> <li>• vomiting</li> <li>• poor feeding</li> <li>• tachypnea</li> <li>• lethargy</li> </ul> <p><b>AND</b></p> <p><math>\geq 1</math> new finding of</p> <ul style="list-style-type: none"> <li>• histopathologic confirmation of myocarditis<sup>b</sup></li> <li>• cMRI findings consistent with myocarditis<sup>c</sup> in the presence of troponin level above upper limit of normal (any type of troponin)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• No other identifiable cause of the symptoms and findings</li> </ul>
<b>Acute pericarditis<sup>d</sup></b>	<p>Presence of <math>\geq 2</math> new or worsening of the following clinical features:</p> <ul style="list-style-type: none"> <li>• acute chest pain<sup>e</sup></li> <li>• pericardial rub on exam</li> <li>• new ST-elevation or PR-depression on EKG</li> <li>• new or worsening pericardial effusion on echocardiogram or MRI</li> </ul>	
<b>Myopericarditis</b>	<p>This term may be used for patients who meet criteria for both myocarditis and pericarditis.</p>	

Source: Sponsor's Clinical Overview, mRNA-1273-P203, Section 7.5.5.

Abbreviations: AV = atrioventricular; cMRI = cardiac magnetic resonance imaging; ECG/EKG = electrocardiogram.

Note: An independent CEAC comprising medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for "probable" or "confirmed" events (Gargano et al 2021) and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.

a. Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).

b. Using the Dallas criteria (Aretz 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

c. To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) AV nodal conduction delays or intraventricular conduction defects. Using either the original or the revised Lake Louise criteria (Ferreira et al. 2018).

d. Adler et al 2015.

e. Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.