



## Review Memorandum Addendum

**Date:** April 28, 2023

**To:** The File

**From:** David C. Kaslow, MD (Director, OVRP)

**Through:** Peter Marks, MD, PhD (Director, CBER)

**Applicant name:** Pfizer-BioNTech Inc.

**Application Number:** EUA 27034

**Product:** Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)

**Subject:** Addendum to CBER’s review memorandum supporting the April 18, 2023, EUA action. This addendum documents FDA’s determination to amend the existing EUA to provide for the administration of additional doses in immunocompromised individuals 6 months through 4 years of age.

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### I. Background

The Pfizer-BioNTech COVID-19 Vaccine (also referred to as BNT162b2 in this document) is a nucleoside-modified messenger RNA (mRNA) vaccine encoding the full-length spike (S) protein of the original (ancestral/reference) Wuhan-Hu-1 SARS-CoV-2 strain. BNT162b2 was initially authorized under EUA on December 10, 2020, for a two-dose primary series vaccination of individuals 16 years of age and older. FDA has subsequently revised the EUA on multiple occasions, including (1) to authorize a third dose of BNT162b2 administered at least 28 days following the two dose series of this vaccine in individuals 5 years of age or older who have undergone solid organ transplantation, or individuals 5 years of age or older who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise,<sup>1</sup> and (2) on June 17, 2022 to authorize the administration of BNT162b2 as a 3-dose primary series for the prevention of COVID-19 in individuals 6 months through 4 years of age. The June 17, 2022, authorization did not provide for an additional primary series dose for immunocompromised

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<sup>1</sup> FDA authorized this dosing regimen on different dates for different age groups. For individuals 12 years of age and older, FDA took this action on August 12, 2021. For individuals 5 through 11 years of age, FDA took this action on January 3, 2022.

individuals 6 months through 4 years of age in part because the authorized primary series already encompassed three doses, and the safety of a fourth dose in this young population was not yet established.

Since then, however, FDA has taken EUA actions that have caused us to reconsider whether it would be appropriate to provide for a modified dosing regimen for immunocompromised individuals 6 months through 4 years of age. First, on March 14, 2023, FDA authorized Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for use in individuals 6 months through 4 years of age to provide a single booster dose at least 2 months after completion of primary vaccination with 3 doses of BNT162b2. In doing so, we reviewed data supporting the safety of a fourth COVID-19 vaccine dose (3 mcg of modRNA) in individuals 6 months through 4 years of age. Second, on April 18, 2023, FDA amended the emergency use authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine, Bivalent to simplify the vaccination schedule for most individuals. This action also included consolidation of the fact sheets and allowed for the use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent for all doses administered to individuals 6 months of age and older, including for an additional dose or doses for certain populations. Through this action, we comprehensively reviewed the dosing schedule for COVID-19 vaccination.<sup>2</sup>

This document serves as an addendum to CBER’s memorandum that supported the April 18, 2023, EUA for Pfizer-BioNTech COVID-19 Vaccine, Bivalent and documents FDA’s determination to amend the existing EUA to provide for the administration of additional doses in immunocompromised individuals 6 months through 4 years of age. With this action, our EUA will provide for a modified dosing regimen for immunocompromised individuals 6 months of age and older who receive the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (including those who previously received BNT162b2).

## **II. Discussion**

A previous review of data led to authorization of a third primary series dose of the BNT162b2 as a part of the previously-authorized regimen for individuals at least 5 years of age who had undergone solid organ transplantation, or who were diagnosed with conditions that are considered to have an equivalent level of immunocompromise. Those data, as well as more recent data, were reviewed in consideration of authorizing additional doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent for immunocompromised individuals 6 months through 4 years of age. Some of those data are described below.

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<sup>2</sup> Also, as part of this action, FDA revised the EUA such that the monovalent BNT162b2 vaccine is no longer authorized for use in the United States. Instead, the Pfizer-BioNTech COVID-19 Vaccine, Bivalent is authorized for use in the United States.



## **IIA. Immunogenicity and Safety 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**

In a clinical study (Study C4591048, Sub study B, Group 2), a subset of 60 participants 6 months through 4 years of age received a booster dose (fourth dose) of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (3 µg modRNA:1.5 µg BNT162b2 Original and 1.5 µg BNT162b2 Omicron BA.4/BA.5 components) after receiving 3 prior doses of Pfizer-BioNTech COVID-19 Vaccine (3 µg modRNA BNT162b2 Original). A subset of 60 participants 6 months through 4 years of age from Study C4591007 who received a third 3 µg dose of Pfizer-BioNTech COVID-19 Vaccine and were closest in match by age, prior SARS-CoV-2 infection status (i.e., before Dose 3), and prior dosing interval (i.e., between Pfizer-BioNTech COVID-19 Vaccine Dose 2 and Dose 3) to participants from Study C4591048, Substudy B, Group 2, served as a reference group.

Regardless of age, prior SARS-CoV-2 infection, or sampling time point, the neutralizing antibody GMTs against the Omicron BA.4/BA.5 variant were 2.2-3.7 times higher in the bivalent vaccine group than in the reference group. Overall, the rise in GMT from prevaccination to 1 month post vaccination was similar across age subgroups (i.e., 6-23 months old, 2-4 years old) and vaccine groups (i.e., post-bivalent vaccine [Dose 4], post-BNT162b2 primary Dose 3). Regardless of the vaccine received, the rise in GMT from prevaccination to 1 month post dose was higher in the children without evidence of previous SARS-CoV-2 infection than children with evidence of previous infection (10-14 vs. 3-5), but the rise was about three times higher in children receiving Pfizer-BioNTech COVID-19 Vaccine, Bivalent. No formal statistical comparisons of the immune response between subsets from the two studies were conducted. Furthermore, review of safety data suggested that the frequencies of solicited local and systemic reactions after a fourth dose of 3 µg Pfizer-BioNTech COVID-19 Vaccine, Bivalent were similar to frequencies within the respective age groups reported after completion of a Pfizer-BioNTech COVID-19 Vaccine three-dose series. These safety data also provide support for the use of additional vaccine administration in immunocompromised individuals 6 months to 4 years of age. This study also provides support for expecting a likely increase in immune response against SARS-CoV-2 in individuals 6 months through 4 years of age following administration of a fourth dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent after three previous doses (either BNT162b2 or Pfizer-BioNTech COVID-19 Vaccine, Bivalent).

Please refer to section 6 of the [EUA memorandum dated March 14, 2023](#) for a detailed review of this study.



## **II B. Immunogenicity of a Third Primary Series Dose of Pfizer-BioNTech COVID-19 Vaccine in Individuals with Certain Kinds of Immunocompromise<sup>3</sup>**

Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine in individuals 6 months through 17 years of age with immunocompromise have been extrapolated from adult data. The immunogenicity of a third primary series dose of Pfizer-BioNTech COVID-19 vaccine was evaluated retrospective in a single-arm study of 101 individuals [mean ( $\pm$ SD) age, 58 $\pm$ 2 years] who had undergone various solid organ transplant procedures (heart, kidney, liver, lung, pancreas) 97 $\pm$ 8 months previously (Kamar N, Abravanel F, Marion O, et al. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med*). A third dose of the Pfizer-BioNTech COVID-19 vaccine was administered to 99 of these individuals approximately 2 months after they had received a second dose. Of 59 transplant recipients who had been seronegative before the third dose, 26 (44%) were seropositive at 4 weeks after the third dose. All 40 patients who had been seropositive before the third dose were still seropositive 4 weeks later. The prevalence of anti-SARS-CoV-2 antibodies was 68% (67 of 99 patients) 4 weeks after the third dose.

This study suggested that administration of a third dose of the Pfizer-BioNTech COVID-19 Vaccine to adult solid-organ transplant recipients increased antibody responses. These adult data support the extrapolation of effectiveness of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent in severely immunocompromised individuals 6 months of age to 17 years of age.

Please refer to the [EUA Memorandum dated August 12, 2021](#) for detailed review.

## **II. C. Literature Evidence on Immunogenicity of a Fourth Dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in Adults:**

A recent (published 23 MAR 2023) systematic review of 24 studies in the literature reported the humoral responses and outcomes after a fourth dose of mRNA vaccines administered to person with compromised immunity. The time frame between the third and fourth dose was reported by 19 studies and ranged from 22 to 201 days. While not all studies reported a ratio of pre- and post-fourth dose antibody titers, all twenty-four studies demonstrated an increase of antibody titers after a fourth dose, both in patients who had a serological strong response and in those who had a weak response after a third dose. No serious adverse events after a fourth dose were reported in the 13 studies that included a safety summary. COVID-19 infection after a fourth dose ranged from 0 to 21%. Overall, all the authors recommended the fourth dose of vaccine against COVID-19 in immunocompromised patients, except for Karaba and Thomson et al. (Reference: [Frontiers | Humoral response after a fourth dose of SARS-CoV-2 vaccine in immunocompromised patients. Results of a systematic review \(frontiersin.org\)](#)).

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<sup>3</sup> Certain kinds of immunocompromise refers to individuals who have undergone solid organ transplant or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.



Of the 24 studies, all but one included the use of Pfizer-BioNTech COVID-19, Vaccine. Ten studies, with a total of 244 patients, exclusively studied a fourth dose of Pfizer-BioNTech COVID-19 Vaccine. This current available evidence from studies of Pfizer-BioNTech COVID-19 Vaccine support the need for and safety and effectiveness of a fourth dose in individuals with compromised immunity.

Based on the totality of evidence, including the current available evidence after a fourth dose of Pfizer-BioNTech COVID-19 Vaccine in immunocompromised adults, vaccine effectiveness of additional doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in certain immunocompromised individuals is extrapolated from Pfizer-BioNTech COVID-19 Vaccine effectiveness inferred from immunogenicity evidence in those immunocompromised individuals. Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent in severely immunocompromised individuals 6 months through 4 years of age are extrapolated from adult data.

### **III. Conclusion:**

For the reasons described in this addendum, it is reasonable to extrapolate the effectiveness in adults to children with these certain kinds of immunocompromise who would have a similar need for and benefit from an additional dose as demonstrated in adults. Additionally, based on available safety and immunogenicity data for three doses of Pfizer- BioNTech COVID-19 Vaccine followed by a fourth dose of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in children, and available safety data from post-authorization experience with additional doses of mRNA vaccines in immunocompromised adults, it is reasonable to extrapolate to conclude a favorable benefit-risk balance for use of an additional dose, administered at least 1 month after the third dose, in individuals 6 months through 4 years of age with certain kinds of immunocompromise and additional doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent that may be administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances. Immunocompromised individuals are at increased risk for severe illness and could benefit from the immune response provided by the modified dosing regimen.

Based on the totality of available scientific evidence, including the data and information discussed in the review memorandum that supported the April 18, 2023, EUA for Pfizer-BioNTech COVID-19 Vaccine, Bivalent and this addendum to that memorandum, it is reasonable to conclude that:

- A fourth dose (0.2 mL) with Pfizer-BioNTech COVID-19 Vaccine, Bivalent, administered at least 1 month following the most recent dose to individuals 6 months through 4 years of age with certain kinds of immunocompromise who have received three previous doses with Pfizer-BioNTech COVID-19 Vaccine or Pfizer-BioNTech COVID-19 Vaccine, Bivalent, 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;



- Subsequent additional 0.2 mL doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent administered to such individuals at the discretion of the healthcare provider 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; and
- The known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine, Bivalent, outweigh the known and potential risks, when administered as a fourth dose (0.2 mL) at least 1 month following the most recent dose to individuals 6 months through 4 years of age with certain kinds of immunocompromise who have received three previous doses with Pfizer-BioNTech COVID-19 Vaccine or Pfizer-BioNTech COVID-19 Vaccine, Bivalent, and when administered as a subsequent additional 0.2 mL dose to such individuals at the discretion of the healthcare provider.