Review Memorandum

Date:	**August 12, 2021**
To:	**The File**
From:	**David Cho, PhD (CBER/OD)**
Through:	**Peter Marks, MD, PhD (CBER/OD)**
Applicant name:	**Pfizer-BioNTech**
Application Number:	**EUA 27034**
Product:	**Pfizer-BioNTech COVID-19 Vaccine**
Subject:	**CBER Assessment of third dose of Pfizer-BioNTech COVID-19 Vaccine (0.3 ml) administered at least 28 days following the first two doses of this vaccine to individuals who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise**

This memorandum provides a summary, review, and recommendation on the submission by Pfizer to amend the emergency use authorization (EUA) of their COVID-19 vaccine to authorize administration of a third dose of the vaccine to certain immunocompromised individuals age 12 years or older who have received two doses of the Pfizer-BioNTech COVID-19 vaccine and who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

Executive Summary

Pfizer has provided a proposed Amendment to EUA 27034 to amend the emergency use authorization (EUA) to include a third dose of the Pfizer-BioNTech COVID-19 vaccine for certain immunocompromised individuals. Reference is made to the EUA for Pfizer-BioNTech COVID-19 Vaccine issued on December 11, 2020, which describes the safety and effectiveness of this vaccine based on a large placebo-controlled randomized trial. Pfizer's currently authorized indication is for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals age 12 years and older. The proposed additional indication for this submission is: Individuals at least 12 years of age who have received two doses of the Pfizer-BioNTech COVID-19 vaccine and who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise, may receive a third dose of the Pfizer-BioNTech COVID-

19 vaccine (0.3 ml) administered at least 28 days following the second dose of the two dose regimen of this vaccine.

Review

The data presented in the request for an EUA amendment are based on published literature [Kamar N, Abravanel F, Marion O, et al. (2021), Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. *NEJM*. DOI: 10.1056/NEJMc2108861] reporting that the standard two dose regimen of vaccination with mRNA-based COVID-19 vaccines may produce suboptimal immunogenicity in solid organ transplant recipients. Investigators stipulate that the use of a third vaccine dose in these individuals may improve the immune response in these individuals, and by extension those who are considered to have an equivalent level of immunocompromise, without a significant change in the safety profile. The paper describes a single arm study conducted in 101 individuals who had undergone various solid organ transplant procedures (heart, kidney, liver, lung, pancreas) a median of 97±8 months previously. A third dose of Pfizer-BioNTech COVID-19 vaccine was administered to 99 of these individuals approximately 2 months after they received a second dose. Levels of total SARS-CoV-2 binding antibodies meeting the pre-identified criteria for success occurred four weeks after the third dose of the Pfizer-BioNTech COVID-19 vaccine in 26/59 (44.0%) of those who were initially considered to be seronegative; 67/99 (68%) of the entire group receiving a third vaccination had an increase in antibody titers that the investigators considered significant. In those who received a third vaccine dose, the adverse event profile was similar to that after the second dose, and no grade 3 or grade 4 events were reported.

CBER also reviewed a supportive and confirmatory paper, exclusively using a similar mRNA COVID vaccine (Moderna COVID-19 vaccine) written by Hall et al. (Hall VG, Ferreira VH, Ku T, et al. (2021). A Randomized Trial of Third Dose mRNA-1273 Vaccine in Transplant Recipients. *NEJM* DOI: 10.1056/NEJMc2111462*)* describes a double-blind, randomized-controlled study conducted in 120 individuals who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years previously (range 1.99-6.75 years). A third dose of the Moderna COVID-19 vaccine was administered to 60 individuals approximately 2 months after they had received a second dose of the same vaccine (i.e., doses at 0, 1 and 3 months); saline placebo was given to 60 individuals for comparison. The primary outcome was anti-RBD antibody at 4 months greater than 100 U/mL. This titer was selected based on NHP challenge studies as well as a large clinical cohort study to indicate this antibody titer was possibly protective. Secondary outcomes were based on a virus neutralization assay as well as polyfunctional T cell responses. Baseline characteristics were comparable between the two study arms as were pre-intervention anti-RBD titer and neutralizing antibodies. Levels of SARS-CoV-2 antibodies indicative of a significant response occurred four weeks after the third dose in 33/60 (55.0%) of the Moderna COVID-19 vaccinated group and 10/57 (17.5%) of the placebo individuals. In the 60 individuals who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 events were reported.

Additional literature reviewed included background information on COVID-19 vaccine regimens in solid organ transplant and hemodialysis patients demonstrating a notable suboptimal response to vaccination in the solid organ transplant population (Carr et al, Review of Early Immune Response to SARS-CoV-2 Vaccination Among Patients With CKD, Kidney Int Rep; 2021, doi:10.1016/j.ekir.2021.06.027); and a study of multiple vaccines in solid organ transplant recipients that did not study a sufficient number of

individuals with a given vaccine regimen to interpret effectiveness (Werbel et al. Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. Ann Int Med; 2021, doi:10.7326/L21-0282)

Recommendation

FDA has been continuously reviewing the literature for information on the safety and efficacy of vaccines to prevent COVID-19 in the immunocompromised. The data from the primary paper (Kamal et al.) show that administration of a third dose of the Pfizer-BioNTech COVID-19 vaccine appears to be only moderately effective in increasing total antibody titers in the individuals studied. It is also unclear whether the antibodies generated from the third dose are protective. Since the third dose of vaccine can lead to a false sense of protection, individuals who receive the third dose should continue barrier measures and the close contacts of immunocompromised persons should be vaccinated as appropriate for their health status. There were no serious adverse events mentioned by the authors in this report. Despite the moderate enhancement in antibody titers, the totality of data (including the supportive paper by Hall et al and demonstrated efficacy of the product in the elderly and persons with co-morbidities) supports the conclusion that a third dose of the Pfizer-BioNTech COVID-19 vaccine may be effective in this population, and that the known and potential benefit of a third dose of Pfizer-BioNTech COVID-19 vaccine dose outweigh the known and potential risks of the vaccine for immunocompromised individuals at least 12 years of age who have received two doses of the Pfizer-BioNTech COVID-19 vaccine and who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise. We conclude that administration to individuals 12 years of age and older is justified, as it was determined in prior studies of the Pfizer-BioNTech COVID-19 vaccine in the 12-15 year age range that the immune response and safety profile was similar to that in individuals 16 years of age and older.

Regarding "the equivalent level of immunocompromise" statement, FDA recognizes that there are a myriad of different immunocompromising conditions. Solid organ transplant patients are immunosuppressed because they are taking a variety of immunosuppressive medications such as cyclosporin, tacrolimus, sirolimus, mycophenolate, azathioprine, and anti-thymocyte globulin. These immunosuppressive medications are used in a variety of other conditions to address immune dysregulation. The effects of these drugs in these other conditions are very similar to the effects in those who have undergone solid organ transplantation: that is there is interference with the cellular and humoral immune response. Thus, individuals receiving these medications whether in the setting for solid organ transplant or for the treatment of immune dysregulation likely both have a similarly attenuated response to the administration of vaccines to prevent COVID-19. Conversely, it is reasonable to extrapolate that the administration of an additional dose of a COVID-19 vaccine to these individuals with immune dysregulation may produce similar responses to those seen in solid organ transplant. It is also reasonable to make the extrapolation that individuals with inherited or acquired conditions that produce reduction in the cellular or humoral immune response similar to that seen in solid organ transplant may produce similar immune responses to a third dose of a COVID-19 vaccine. We therefore believe it is appropriate to amend the authorization to include a third dose of the vaccine for individuals at least 12 years of age who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.