Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Epidemiology (OBE)
Division of Epidemiology (DE)

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

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To:	Ramachandra Naik, PhD Chair, Review Committee Office of Vaccines Research and Review (OVRR), CBER, FDA
Through:	Manette Niu, MD Branch Chief, AEB DE, OBE, CBER, FDA Narayan Nair, MD Division Director, DE OBE, CBER, FDA
Subject:	Review of Pharmacovigilance Plan
Sponsor:	Pfizer
Product:	BNT162b2 (COVID-19 Vaccine)
BLA Number:	125742/0
Proposed Indication:	Active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals $\geq$16 years of age.
Submission Date:	May 18, 2021
Action Due Date:	January 16, 2022

1 Objective and Scope

The purpose of this review is to assess the adequacy of the sponsor's proposed pharmacovigilance plan (PVP) submitted under the original BLA 125742/0 for post-marketing safety monitoring for BNT162b2 (COVID-19 vaccine) and to identify potential safety issues associated with the use of BNT162b2 that may need to be addressed through additional pharmacovigilance activities including safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) or a Risk Evaluation and Mitigation Strategy (REMS).

2 Product Information

2.1 Product Description

BNT162b2 contains a nucleoside-modified messenger RNA (modRNA) that encodes the viral spike (S) glycoprotein of SARS-CoV-2. Each vial of vaccine is diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose includes the following ingredients: lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol), potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, and sucrose.

2.2 Authorized Indication and Dosing Regimen

The Pfizer-BioNTech COVID-19 Vaccine is currently authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals ≥12 years of age. The vaccine is administered intramuscularly as a series of two doses (0.3 mL each) given three weeks apart.

2.3 Proposed Product Indication and Dosing Regimen

The proposed indication for BNT162b2 is active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals ≥16 years of age. The vaccine is administered intramuscularly as a series of two doses (0.3 mL each) given three weeks apart.

3 Materials Reviewed

- Pharmacovigilance Plan, Version 1.0 (STN 125742/0.1, Module 1.16.1, dated May 17, 2021; received May 18, 2021)
- Pharmacovigilance Plan, Version 1.1 (STN 125742/0.20, sequence 0021, Module 1.16.1, dated July 28, 2021; received July 29, 2021)

- Cumulative Analysis of Post-authorization Adverse Event Reports (STN 125742/0, Module 5.3.6, received May 6, 2021)
- Summary of Clinical Safety (STN 125742/0, Module 2.7.4; received May 6, 2021)
- Draft Labeling Text (STN 125742/0.1, Module 1.14; received May 18, 2021)
- Post-authorization safety surveillance study protocols linked in the PVP
- Sponsor's IR responses
- VAERS database and data mining

4 Summary of Pertinent Regulatory History and Prior Marketed Experience

Pertinent regulatory history is shown in Table 1. BNT162b2 has received temporary authorization for emergency supply in 28 countries and conditional marketing authorization in 39 countries. As of August 4, 2021, over 194 million doses of BNT16b2 have been administered to over 88 million individuals in the U.S. under the EUA. Per the sponsor's Summary Monthly Safety Report (STN 19736.409), approximately (b) (4) doses of BNT162b2 have been shipped worldwide from December 1, 2020 through June 30, 2021, which corresponds to approximately 757,863,718 estimated doses administered.

Table 1: Pertinent Regulatory History

Date	Regulatory Action
April 29, 2020	IND for BNT162b2 became effective
July 7, 2020	Fast Track Designation granted for individuals 18 years of age and older
December 11, 2020	Emergency Use Authorization (EUA 27034) granted for active immunization to prevent COVID-19 in individuals 16 years of age and older
May 10, 2021	FDA re-issued EUA letter to expand authorization for use in individuals 12 through 15 years of age with addition of following warning in Fact Sheet for Healthcare Providers: "Syncope (fainting) may occur in association with administration of injectable vaccines, in particular adolescents. Procedures should be in place to avoid injury from fainting."
May 18, 2021	Final roll of BLA 125742/0 submitted
June 25, 2021	EUA Fact Sheet revised to add Warnings for myocarditis and pericarditis following use of Pfizer-BioNTech COVID-19 Vaccine

5 Summary of Sponsor's Safety Database

5.1 Clinical Studies

There are two clinical studies for BNT162b2 which are summarized in Table 2.

Table 2: Summary of Clinical Studies for BNT162b2*

Study	Description	Number of subjects randomized	Data cut-off date
BNT162-01	Phase 1/2 first in human dose finding study, open-label, non-randomized, included two age cohorts: 18-55 years and 56-85 years; BNT162b2 was given at 5 dose levels (1, 3, 10, 20, 30 µg)	216	October 23, 2020
C4591001 (BNT162-02)	Phase 1/2/3 randomized, placebo-controlled, observer blind study for safety, immunogenicity, and efficacy		
	Phase 1: two age cohorts: 18-55 years and 65-85 years; 3 dose levels for BNT162b2: 10, 20, and 30 µg, randomized 4:1 to receive active vaccine or placebo; long term follow-up (LTFU) for AEs/SAEs for BNT162b2 30 µg group only	195 (30 in LTFU)	August 24, 2020 (March 13, 2021 for LTFU)
	Phase 2: two age cohorts: 18-55 years and 56-85 years; BNT162b2 30 µg dose; randomized 1:1 to receive active vaccine or placebo	360	September 2, 2020
	Phase 3: three age cohorts: 12-15, 16-55 years and >55 years; BNT162b2 30 µg dose; randomized 1:1 to receive active vaccine or placebo	43,847 (includes 360 subjects from Phase 2)	March 13, 2021

*Adapted from sponsor's Summary of Clinical Safety, Table 1.

Study BNT162-01

Study BNT162b2 is an ongoing, first-in-human, open-label, non-randomized Phase 1/2 dose finding and cohort expansion (for dose levels selected during dose finding) study conducted in Germany (not under U.S. IND) among healthy adults age 18 to 85 years of age. Four vaccine candidates from three different RNA platforms were tested. Key safety assessments included physical examinations, electrocardiograms, clinical laboratory tests, solicited local and systemic reactions (recorded in diaries for seven days post-dose), SARS-CoV-2 testing, adverse events (AEs), and serious adverse events (SAEs). Unsolicited treatment emergent AEs (TEAEs) were recorded for 28 days post-second dose. Adverse events of special interest (AESI) included enhanced respiratory disease or flu-like symptomatology that did not resolve after seven days.

Study C4591001

Study C4591001 (IND 019736) is a Phase 1/2/3 randomized, placebo-controlled, observer blind study for safety, immunogenicity, and efficacy. Participants are followed for 24 months. Participants $\geq$16 years who originally received placebo (i.e., normal saline) and became eligible for receipt of BNT162b2 were offered BNT162b2 in a phased process as part of the study.

Phase 1 evaluated two vaccine candidates (BNT162b1 and BNT162b2) and involved dose-level finding (three dose levels for BNT162b2: 10, 20, and 30 µg) among two age cohorts of healthy adults (18-55 and 65-85 years; n=195). Subjects were randomized 4:1 to receive active vaccine or placebo. Reactogenicity (i.e., local and systemic reactions) was assessed for up to seven days after each dose, AEs were assessed from dose 1 through 1-month after the last dose, and SAEs were assessed from dose 1 to six months after the last dose. Long-term follow-up for AEs and SAEs was conducted for the BNT162b2 30 µg cohort (n=30) from 1-month post-second dose to the unblinding date (approximately 6-months post-second dose).

Phase 2/3 was conducted to define the safety profile of BNT162b2 and involved administration of BNT162b2 (30 µg dose) to individuals in three age cohorts (12-15 years, 16-55 years and >55 years; n=43,847). Phase 2/3 participants were those judged by investigators to be at higher risk for acquiring COVID-19 (e.g., individuals who use mass transportation or frontline essential workers). Subjects were randomized 1:1 to receive active vaccine or placebo. Phase 2 was conducted to confirm the safety profile seen in Phase 1 and included the first 360 randomized subjects; reactogenicity was assessed for up to seven days after each dose and AEs/SAEs were assessed from dose 1 to 7-days post-second dose. Phase 3 assessed reactogenicity in a subset of subjects (n=9,839) for up to seven days after each dose. Adverse events and SAEs were assessed in all subjects for 1-month post-second dose and up to the unblinding

date. In addition, open-label AEs/SAEs were assessed among participants originally randomized to BNT162b2 (n=20,309) from the date of unblinding to the data cut-off (March 13, 2021). Open-label AEs/SAEs were assessed among participants who were originally randomized to placebo but were vaccinated with BNT162b2 after treatment disclosure (n=19,525) from the date of BNT162b2 vaccination to the data-cutoff (March 13, 2021). No AEs of special interest were defined for Study C4591001.

5.2 Adverse Events

In Study BNT162-01 most solicited local and systemic reactions were mild or moderate in severity and were short-lived after dosing. Most unsolicited AEs were also mild to moderate in severity and all resolved; there were no unanticipated safety findings. There were no AESIs, deaths, or treated-related SAEs reported among participants who received BNT162b2 in Study BNT162-01. Similarly, in Phase 1 and 2 of Study C4591001, reactogenicity was mostly mild to moderate and short-lived after dosing; the AE profile did not suggest any serious safety concerns. There were no treatment-related SAEs or deaths.

In Phase 3 of Study C4591001, solicited local reactions occurred more commonly in the BNT162b2 group as compared with the placebo group; the majority of local reactions were mild or moderate in severity after both first and second doses and in both younger (≤55 years) and older age groups (>55 years). Solicited systemic events and use of antipyretic/pain medication were generally reported less frequently in the placebo group as compared with the BNT162b2 group for both age groups and doses, with the exception of vomiting and diarrhea which were reported at similar frequencies between BNT162b2 and placebo groups. The majority of solicited systemic events were mild or moderate in severity. Solicited systemic events occurred more frequently after Dose 2 of BNT162b2 as compared with Dose 1 in both younger and older age groups. Reactogenicity AEs were generally milder and less frequent in the older age group as compared with the younger age group.

In the blinded placebo-controlled follow-up period (n=43,847), 30.2% of BNT162b2 recipients and 13.9% of placebo recipients had any AE from Dose 1 to 1-month after Dose 2 and 0.6% and 0.5%, respectively, had an SAE; there were three deaths in the BNT162b2 group and five deaths in the placebo group. The most frequently reported AEs were reactogenicity events including injection site pain (13.3% BNT162b2 group vs 1.8% placebo group), pyrexia (6.9% vs 0.4%), fatigue (6.7% vs 1.7%), chills (6.2% vs 0.5%), headache (6.1% vs 1.9%), myalgia (5.7% vs 0.8%), pain (2.9% vs 0.3%), and arthralgia (1.2% vs 0.5%). Among those in the BNT162b2 group, the overall AE frequencies were higher in the younger age group (32.6%) as compared with the older age group (26.7%).

From Dose 1 to the unblinding date, the AEs with the highest incidence rates were consistent with the AEs in the Dose 1 to 1-month after Dose 2 analysis. There were also similar incidence rates of SAEs (3.2 per 100 person-years for BNT162b2 group vs 3.3 per 100 person-years for placebo group) and deaths among BNT162b2 and placebo

recipients (0.2 per 100 person-years for both groups; 15 vs 14 deaths, respectively). There were four related-SAEs in the BNT162b2 group (one each of lymphadenopathy, shoulder injury related to vaccine administration, ventricular arrhythmia, and paresthesia of right leg) and one related-SAE in the placebo group (psoriatic arthropathy). The 15 deaths in BNT162b2 group were due to: cardiac arrest (n=4), arteriosclerosis (n=2), and one each of COVID-19 pneumonia, cardiac failure congestive, cardiorespiratory arrest, chronic obstructive pulmonary disease (COPD), emphysematous cholecystitis, hypertensive heart disease, metastatic lung cancer, sepsis, septic shock, shigella sepsis, and an unevaluable event; multiple contributing causes of death could be reported for each subject. The 14 deaths in the placebo group were due to COVID-19 (n=2), multiple organ dysfunction syndrome (n=2), myocardial infarction (n=2), pneumonia (n=2), lacking specific cause (n=2; one "death" and one "missing") and one each of acute respiratory failure, aortic rupture, metastatic biliary cancer, cardiac arrest, cardiorespiratory arrest, dementia, hemorrhagic stroke, liver metastases, and overdose. None of the deaths during the Dose 1 to unblinding date time period were assessed by investigators as related to the study intervention.

From the unblinding date to the data cut-off, the incidence rates of AEs were markedly reduced relative to the AEs reported from Dose 1 to the unblinding date among the original BNT162b2 recipients (n=21,926) (8.8/100,000 person-years vs 83.2/100,000 person-years, respectively). There were 55 SAEs during this time period among the original BNT162b2 recipients, including one related-SAE of myocardial infarction (participant in younger age group with no past medical history [PMH], onset 71-days after Dose 2, resolved same day). There were three deaths among the original BNT162b2 participants (all in the older age group; one each due to road traffic accident, lung metastases, and myocardial infarction); none of the deaths were assessed by investigators as related to study intervention.

Among the 19,525 participants who originally received placebo and then received BNT162b2 after unblinding, the most frequently reported AEs overall were related to reactogenicity and were consistent with AEs reported among the group that was originally randomized to receive BNT162b2. After vaccination with BNT162b2, there was one related-SAE of anaphylactoid reaction in a patient with an ongoing medical history of drug hypersensitivity and food and seasonal allergies (onset 2-days post-1st dose of BNT162b2; treated with self-administered epinephrine pen and resolved same day). Two deaths occurred following vaccination with BNT162b2 (both in the older age group; one each due to cardiorespiratory arrest and completed suicide), neither of which were assessed by investigators as related to the study intervention.

The sponsor also provided a review of AEs of interest requested by FDA (hypersensitivity/anaphylaxis, Bell's palsy/facial paralysis, lymphadenopathy, and appendicitis) and the Center for Disease Control and Prevention's (CDC) AESI list for COVID-19 vaccines. This review was focused on the Dose 1 to unblinding time period. For hypersensitivity, there was a higher number and percentage of participants in the BNT162b2 vs placebo groups (182 [0.83%] vs 161 [0.73%], respectively), which was mainly due to skin and subcutaneous tissue disorders (134 [0.61%] vs 119 [0.54%]),

including rash (62 [0.28%] vs 52 (0.24%]), urticaria (18 [0.08%] vs 15 [0.07%]), rash pruritic (8 [0.04%] vs 6 [0.03%]), rash maculo-papular (7 [0.03%] vs 4 [0.02%]), and eczema (7 [0.03%] vs 3 [0.01%]). There were three hypersensitivity SAEs during the blinded placebo-controlled follow-up period: two in the BNT162b2 group (anaphylactic reaction following bee sting and drug hypersensitivity to an antibiotic) and one in the placebo group (anaphylactic shock due to an ant bite); none were considered by investigators as related to the study intervention. Among the original placebo group participants who then received BNT162b2 after unblinding there was one anaphylactoid reaction (assessed as related; reviewed in section 5.2 of this memorandum). For Bell's palsy, there were four cases in the BNT162b2 group (two of which were considered related by investigators) and two in the placebo group during the blinded placebo-controlled follow-up period. Among those who originally received placebo and then received BNT162b2 after unblinding, there were three participants who experienced facial paralysis (all considered related by investigators). Lymphadenopathy was reported in 87 (1.0 per 100 person-years [PY]) participants in the BNT162b2 group compared to 8 (0.2 per 100 PY) participants in the placebo group. One lymphadenopathy event (right axilla, normal lymph node biopsy) was considered a related-SAE in the BNT162b2 group and resolved within 66 days. Appendicitis was reported for a total of 15 BNT162b2 participants, including one case of perforated appendicitis, as compared with 12 total reports of appendicitis in the placebo group, including two cases of complicated appendicitis, and one case of perforated appendicitis. All appendicitis cases were reported as SAEs and none were considered related to study intervention by investigators. Among CDC-defined AESIs that occurred from Dose 1 to unblinding in the Phase 2/3 study, the overall number and percentage of participants with any unsolicited AESIs within selected SMQs were similar between the BNT162b2 (224 [1.02%]) and placebo groups (217 [0.99%]); most individual AESI categories were similar between BNT162b2 and placebo groups (or higher in the placebo group) with the exception of hypersensitivity which is discussed above.

Reviewer comment: The sponsor submitted a revised PVP (Version 1.1) on July 29, 2021 which added the important identified risks of myocarditis and pericarditis and also included clinical trial data for myocarditis and pericarditis through June 18, 2021. The revised PVP indicated that among participants age 16 years and older two SAE cases of pericarditis were found from Phase 3 clinical trial C4591001; both SAEs were deemed by study investigators as not related to study treatment. There were no clinical trial reports of myocarditis as an SAE. Review of the sponsor's safety data did not identify new safety concerns that required further amending the sponsor's PVP.

5.3 Sponsor's Cumulative Analysis of Post-Authorization Adverse Event Reports

Cumulative post-authorization safety data, through February 28, 2021:

The sponsor provided a summary of cumulative post-authorization safety data, including U.S. and foreign post-authorization adverse event reports received through February 28, 2021. The safety database includes AEs reported spontaneously, by health authorities, and from published medical literature, Pfizer-sponsored marketing

programs, non-interventional studies, and serious AEs reported from clinical studies regardless of causality assessment.

There was a total of 42,086 AE reports containing 158,893 events. Most reports were from the U.S. (13,739), followed by the United Kingdom (13,404), Italy (2,578), Germany (1,973), France (1,506), Portugal (866), and Spain (756); the remaining 7,324 reports were from 56 other countries. Most reports were in females (29,914 (71.1%) reports); there were 9,182 (21.8%) reports for males and 2,990 (7.1%) with no sex data. Reports by age groups were as follows: ≤17 years (n=175), 18-30 years (n=4,953), 31-50 years (n=13,886), 51-64 years (n=7,884), 65-74 years (n=3,098), ≥75 years (n=5,214), and unknown (n=6,876). The most commonly reported MedDRA Preferred Terms (PTs) occurring ≥10% were headache (24.1%), pyrexia (18.2%), fatigue (17.4%), chills (13.1%), vaccination site pain (12.3%), nausea (12.3%), and myalgia (11.7%).

The sponsor included a summary of post-authorization AE reports for each safety concern listed in the PVP (see Section 7 of this memorandum for PVP summary). For anaphylaxis (important identified risk), there were 1,002 cases that met the Brighton Collaboration (BC) definition level 1 (highest level of certainty) through 4 (reported event with insufficient evidence to meet case definition), including nine fatal events. The sponsor concluded that evaluation of these cases did not reveal any significant new safety information and that anaphylaxis and non-anaphylactic hypersensitivity reactions are appropriately described in the product labeling (Sections 4 Contraindications, 5.1 Management of Acute Allergic Reactions, and 6 Adverse Reactions of the proposed USPI). In addition, the sponsor did not identify any cases definitively considered to be vaccine-associated enhanced disease (VAED) or vaccine-associated enhanced respiratory disease (VAERD) and concluded that VAED/VAERD remains a theoretical risk for the vaccine (i.e., important potential risk).

Among “missing information” categories in the PVP, there were 413 reports (84 serious and 329 non-serious) involving use in pregnancy and lactation. There were 270 maternal cases and four fetus/infant cases. Pregnancy outcomes were reported for 32 cases (including twins who each had two different outcomes reported) and included spontaneous abortion (n=23); outcome pending (n=5); premature birth with neonatal death, spontaneous abortion with intrauterine death (2 each); spontaneous abortion with neonatal death and normal outcome (1 each). Among mothers, 124 cases (75 serious and 49 non-serious) were pregnancy-related PTs: spontaneous abortion (n=25); uterine contraction during pregnancy, premature rupture of membranes, abortion, abortion missed, and fetal death (1 each). The four fetus/infant cases reported the following PTs: exposure during pregnancy, fetal growth restriction, maternal exposure during pregnancy, premature baby (2 each); and death neonatal (n=1). There were 133 reports in breastfed infants, including 17 cases (3 serious and 14 non-serious) that reported clinical events that occurred in an infant/child exposed to vaccine via breastfeeding: pyrexia (n=5); rash (n=4); infant irritability (n=3); infantile vomiting, diarrhea, insomnia, and illness (2 each); poor feeding infant, lethargy, abdominal discomfort, vomiting, allergy to vaccine, increased appetite, anxiety, crying, poor quality sleep, eructation, agitation, pain, and urticaria (1 each).

There were 34 reports (24 serious and 10 non-serious) involving 132 AEs indicating use in pediatric individuals <12 years of age. Events reported more than once included product administered to patient of inappropriate age (n=27); off label use (n=11); pyrexia (n=6); product use issue (n=5); fatigue, headache, nausea (4 each); vaccination site pain (n=3); upper abdominal pain, COVID-19, facial paralysis, lymphadenopathy, malaise, pruritis, and swelling (2 each).

There were 1,665 reports concerning vaccine effectiveness (1,649 drug ineffective and 16 vaccination failure). Among the 16 cases of vaccination failure, eight individuals had onset of COVID-19 symptoms within 7-13 days post-2nd vaccine dose and six individuals had onset within 15-29 days post-2nd dose. Six reports were asymptomatic COVID-19 infections. For each concern listed in the PVP, the sponsor concluded that no new safety signals were identified in post-authorization AE data.

The sponsor also evaluated AEs in the following AESI categories: anaphylactic reactions, cardiovascular, COVID-19, dermatological, hematological, hepatic, facial paralysis, immune-mediated/autoimmune, musculoskeletal, neurological (including demyelination), other (e.g., herpes viral infections) pregnancy-related, renal, respiratory, thromboembolic events, stroke, and vasculitic events, and concluded that the cumulative case review did not raise new safety issues.

Finally, the sponsor provided information on reports potentially indicative of medication errors. There were 2,056 reports of medication errors, with or without associated AEs. Of these, there were seven death reports; and 1,569 (76.3%) reports were medically confirmed. The sponsor indicated that all medication errors reported in death reports were assessed as non-serious events with unknown outcomes and concluded that based on available information, including causes of death, the relationship between the medication error and the death is weak. Overall, most reports (n=1,371, 66.7%) included only medication errors without any associated clinical adverse events (e.g., poor quality product administered, product temperature excursion issue, underdose, circumstance or information capable of leading to medication error). In 685 reports, there were AEs co-reported; the most frequent AEs were headache (n=187), pyrexia (n=161), fatigue (n=135), chills (n=127), pain (n=107), vaccination site pain (n=100), nausea (n=89), myalgia (n=88), pain in extremity (n=85), arthralgia (n=68), off label use (n=57), dizziness (n=52), lymphadenopathy (n=47), asthenia (n=46), and malaise (n=41).

Reviewer comment: The sponsor's cumulative summary of post-authorization data as of the data lock point, February 28, 2021, showed that the most frequently reported AEs were consistent with AEs described in the EUA Fact Sheet (i.e., headache, pyrexia, fatigue, chills, vaccination site pain, nausea, and myalgia).

Post-authorization safety data, updated through June/July 2021:

The sponsor submitted a revised PVP (Version 1.1) on July 29, 2021 which included post-authorization data for myocarditis and pericarditis among individuals 16 years of age and older through June 18, 2021. There was a total of 823 AE reports, including 490 reports of myocarditis and 372 reports of pericarditis; 38 reports included both myocarditis and pericarditis. Among the 490 myocarditis reports, 464 (including 78 U.S. reports) met Brighton Collaboration Level 1 to 4 (Version 1.4.2; May 30, 2021). The majority of myocarditis reports (n=325, 66.3%) were in males and the median age was 32 years (range=16-97 years); there were 14 death reports. Among the 371 reports of pericarditis (including 68 U.S. reports), 181 (48.8%) were in males and 185 (49.9%) occurred in females (five reports did not include sex); the median age was 51 years (range=16-92 years) and there were three death reports.

The sponsor also provided post-authorization data through June 18, 2021 for myocarditis and pericarditis in individuals age 12-15 years. There were 13 reports of myocarditis (none were deaths); 11 met Brighton Collaboration Level 4 (i.e., reported event with insufficient evidence to meet the case definition) and two met Brighton Collaboration Level 5 (i.e., not a case); 10 (90.9%) were male and 1 (9.1%) was female; the median age was 14 years (range=12-15 years). There were four reports of pericarditis (none were deaths); all were male, and the median age was 13.5 years (range=12-15 years).

The sponsor indicates that a mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established, however myocarditis and pericarditis are considered an important identified risk in the PVP. The sponsor concluded that the vaccine continues to have a favorable risk benefit balance and that considering the low rates of myocarditis and pericarditis reported following vaccination, balanced with the risk of death and illness (including myocarditis) from SARS-CoV-2, the public health impact of post-vaccination myocarditis and pericarditis is minimal.

Reviewer comment: There are ongoing analyses, by the sponsor and FDA, to further characterize the new safety signal for myocarditis and pericarditis after the Pfizer-BioNTech COVID-19 vaccine. As described above, the majority of myocarditis reports occurred in males, under 30 years of age. Please see section 6.1 and 8.2 for additional discussion.

6 Summary of FDA Post-Authorization Safety Data

6.1 Vaccine Adverse Event Reporting System Data

Since its authorization on December 11, 2021 through June 11, 2021 a total of 151,543 reports, including 24,961 serious reports (3,512 of which were death reports), have been received and processed (coded, redacted, and quality assurance performed) by the Vaccine Adverse Event Reporting System (VAERS) for the Pfizer-BioNTech COVID-19 vaccine. Among all reports the top 10 most frequently reported PTs are headache, fatigue, pyrexia, chills, pain, dizziness, nausea, pain in extremity, arthralgia,

and injection site pain. Among serious reports the top 10 most frequently reported PTs are SARS-CoV-2 test, COVID-19, dyspnea, headache, fatigue, pyrexia, death, SARS-CoV-2 test positive, dizziness, and nausea.

Reviewer comment: Most of the commonly reported PTs in VAERS reports are labeled events in the EUA Fact Sheet (i.e., headache, fatigue, fever, chills, pain, joint pain, nausea, vomiting) or a non-specific AE that could be a possible vaccine stress-related response (i.e., dizziness). The PTs of SARS-CoV-2 test and SARS-CoV-2 test positive refer to testing for SARS-CoV-2 infection. The PT of "dyspnea" is a non-specific symptom that may be present in a variety of conditions both serious and non-serious. Dyspnea associated with FDA/CDC AESIs, such as acute myocardial infarction, pulmonary embolus, or myopericarditis, is monitored as part of routine surveillance for AESIs and/or through death reviews.

VAERS was queried for the safety concerns listed in the PVP (Section 7 of this memorandum).

Anaphylaxis:

For the important identified risk of anaphylaxis, VAERS was queried from December 11, 2020 (the date of authorization) to June 11, 2021. The query was run on June 17, 2021 using the PTs anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, or anaphylactoid shock. The search returned 1,034 reports (1,009 U.S. reports), including 524 serious reports; 12 of the serious reports were death reports. There were 167,680,391 doses of the Pfizer-BioNTech Covid-19 vaccine administered in the U.S. as of June 14, 2021. This equates to a crude reporting rate for anaphylaxis of 6.0 cases per million doses. Among the 12 deaths, five individuals were female, six were male, and one was of unknown sex; the median age was 81 years (range= 58-86 years; 3 individuals were of unknown age) and the median onset as calculated by VAERS dates was zero days post-vaccination (range=0-16 days). Nine individuals who died reported various chronic underlying conditions including hypertension, asthma, diabetes mellitus, ischemic cardiomyopathy, myocardial infarction, atrial fibrillation, arrythmia, obesity, sleep apnea, and dementia. Three individuals who died had a history of hypersensitivity to penicillin, contrast imaging, or food/fruit allergy. One individual had a history of COVID-19 one-month prior to vaccination and one individual was diagnosed with concomitant COVID-19 pneumonia and acute hypoxic respiratory failure post-vaccination.

Reviewer comment: Allergic reactions and anaphylaxis are labeled in the EUA Fact Sheet for this product. In addition, the EUA Fact Sheet cites CDC clinical guidelines which recommend observation periods following COVID-19 vaccination. Review of VAERS reports did not identify new safety concerns related to anaphylaxis. Limitations to interpreting this information include that VAERS data are based on passive surveillance and important limitations of passive surveillance data include missing/inaccurate data, unconfirmed diagnoses, potential under-reporting, and variable or incomplete reporting. The methodology for calculating crude reporting rates was

based on reports retrieved from automated queries, which may include duplicate cases as not all cases were manually reviewed to apply the Brighton Collaboration case definition criteria for anaphylaxis (Ruggeberg, 2007). (Note that this is a key difference in the above methodology compared to previous publications [MMWR Jan 15, 2021; Gee, 2021; Shimabukuro, 2021], which calculated reporting rates based only on adjudicated cases that were confirmed through medical record review or direct contact with the provider.) The incidence of anaphylaxis after receipt of the Pfizer-BioNTech COVID-19 vaccine is comparable with those reported after receipt of other vaccines (Gee, 2021).

Myocarditis and pericarditis:

After the issuance of the EUA, FDA and CDC received reports of myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine. In accordance with FDA recommendations, the sponsor added myocarditis and pericarditis as important identified risks in the PVP. A VAERS search was performed for the timeframe from December 11, 2020 (the date of authorization) to June 21, 2021. The query was run on June 23, 2021 utilizing the PTs autoimmune myocarditis, autoimmune pericarditis, eosinophilic myocarditis, hypersensitivity myocarditis, myocarditis, pericarditis, pericarditis adhesive, pericarditis constrictive, and pleuropericarditis.

The query returned 1,023 reports (1012 U.S. reports), including 809 serious reports (seven were death reports concerning six unique individuals), of which 652 reports were in individuals under 30 years of age. The reports concerned 775 (75.8%) males and 238 (23.3%) females; 10 reports concerned individuals of unknown sex. The median age was 21 years (range=12-86 years). The median onset post-vaccination as calculated by VAERS dates was 3 days (range=0-151 days). The six unique death reports (3 U.S. and 3 foreign reports) concerned three males and three females; the median age at death was 66 years (range=19-81 years) and the median onset post-vaccination was 4 days (range=1-22 days). Four deaths occurred following the second dose, one following the first dose, and for one the dose number was not reported. Most death reports contained limited information or described concurrent medical conditions and/or risk factors that might have contributed to the death. A summary of each death report is listed below:

1394140: 78-year male with no reported PMH died (b) (6) post-2nd vaccine. An autopsy revealed myocarditis, but limited details were provided.

1044420: 36-year male with history of anosmia and influenza-like illness (ILI) developed non-specific ILI symptoms a few days post-vaccination. Twenty-two days post-2nd vaccination he developed low grade fevers, malaise, and sore throat. Testing revealed a negative SARS-CoV-2 test and a positive coronavirus nucleocapsid IgG. His symptoms progressed and the patient ultimately deteriorated and died. Autopsy findings included: heart with multifocal myocarditis with mixed inflammatory infiltrate, myocyte necrosis, microthrombi. The death certificate listed the following causes of death: hemorrhagic shock, d/t intraperitoneal bleed, d/t coagulopathy, d/t post COVID-19 syndrome.

1340821: 60-year female reported to have endocarditis following first dose and then myocarditis post-2nd dose (reported by friend, limited details).

1070309: Foreign report: 72-year female with PMH of cardiac arrest, chest pain, high cholesterol, neoplasm, acute myeloid leukemia, hypertension, high BMI, and GERD had chest pain and pericarditis 3-days post-1st dose. She suffered a cardiac arrest 7-days post-vaccination and died (b) (6) days post-vaccination due to pericarditis.

1048413: Foreign report: 19-year male with no PMH experienced accelerated heartbeat, shortness of breath (SOB), and sharp pains radiating down left arm 5-days post-2nd vaccination. He was hospitalized in intensive care unit (ICU) and died. The reported cause of death was myocarditis.

1048221: Foreign report: 81-year female with history of COVID-19 experienced septic shock, extensive myo- and pericarditis, and multiple organ failure 3-days post-vaccination, died (b) (6) days post-vaccination; autopsy-determined cause of death: Carditis pericardium myocardium.

In addition to review of reports from automated queries, all U.S. death reports are manually reviewed, and the following death was identified:

1406840: 13-year male with attention deficit hyperactivity disorder and developmental coordination disorder experienced flu-like symptoms for (b) (6) days and then was found deceased; onset of symptoms 1-day post-vaccination. The preliminary autopsy report revealed cardiomegaly with biventricular dilatation, bilateral serous pulmonary effusions and serous pericardial effusion, marked pulmonary edema and congestion, and moderate degree of diffuse cerebral edema; SARS-CoV-2 and influenza A/B tests, toxicology, and determination of the cause of death are pending.

Furthermore, observed to expected (O/E) analyses were performed for risk windows of 7 days and 21 days, stratified by age, sex and dose, using U.S. data retrieved from automated queries of the VAERS database (data lock point July 6, 2021). The following PTs were used: atypical mycobacterium, pericarditis, autoimmune myocarditis, autoimmune pericarditis, bacterial pericarditis, coxsackie myocarditis, coxsackie pericarditis, cytomegalovirus myocarditis, cytomegalovirus pericarditis, enterovirus myocarditis, eosinophilic myocarditis, hypersensitivity myocarditis, immune-mediated myocarditis, myocarditis, myocarditis bacterial, myocarditis helminthic, myocarditis infectious, myocarditis meningococcal, myocarditis mycotic, myocarditis post infection, myocarditis septic, pericarditis, pericarditis adhesive, pericarditis constrictive, pericarditis helminthic, pericarditis infective, pericarditis mycoplasmal, pleuropericarditis, purulent pericarditis, viral myocarditis, and viral pericarditis. The vaccine administration data lock point for the O/E analysis was June 30, 2021. Only results for 7-day risk windows are shown in Tables 3 and 4 (relative risks [RR] with 95% CI >1 in **bold** font). The O/E analysis, stratified by age and dose number, indicates that the observed number of cases exceeds the expected number of cases (based on pre-COVID-19 pandemic U.S. population-based background incidence rates). The reporting rate and RR was higher among males than females for

almost all age groups and higher following dose 2 as compared to dose 1 in most age groups for both males and females. This trend was higher in the 7-day risk window compared to the 21-day risk window, and in the younger age groups. Important limitations of passive surveillance data include missing/inaccurate data, unconfirmed diagnosis and potential under-reporting. There is ongoing follow-up of the reports to obtain additional medical records for assessment of cases.

Table 3: Reporting Rates and Relative Risk (RR) of Myocarditis and Pericarditis Post Vaccination in Males using a 7-Day Risk Window

Age Group (years)	Background Rate*	Dose 1 Reporting Rate**	Dose 1 RR[ł] (95% CI)	Dose 2 Reporting Rate**	Dose 2 RR[ł] (95% CI)
12 - 17	2.16 [a]	0.99	**23.94 (17.02-32.73)**	10.22	**246.84 (219.83-276.26)**
18 - 24	2.16	0.48	**11.5 (6.7-18.42)**	5.91	**142.84 (122.17-166)**
25 - 29	2.16	0.26	**6.2 (2.49-12.78)**	1.55	**37.44 (26.08 - 52.06)**
30 - 39	6.1[b]	0.17	1.45 (0.7 -2.67)	0.88	**7.56 (5.49-10.14)**
40 - 49	6.1	0.12	1.04 (0.42-2.13)	0.53	**4.49 (2.93-6.58)**
50 - 64	6.1	0.07	0.59 (0.24-1.22)	0.14	1.16 (0.6-2.03)
≥65	6.1	0.07	0.63 (0.25-1.3)	0.07	0.61 (0.22-1.33)

*Background rates are rates per 100,000 persons per year.
**Reporting rates are per 100,000 doses of vaccine
[ł]Relative Risk (RR) is the reporting rate compared to the background rate when applied to the proportion of individuals vaccinated in each age group to July 1, 2021
[a]Gubernot et al, U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines
[b]Roth et al, Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019

Table 4: Reporting Rates and Relative Risk of Myocarditis and Pericarditis post Vaccination in Females using a 7-Day Risk Window

Age Group (years)	Background Rate*	Dose 1 Reporting Rate**	Dose 1 RR[ł] (95% CI)	Dose 2 Reporting Rate**	Dose 2 RR[ł] (95% CI)
12 - 17	2.16[a]	0.15	**3.51 (1.29-7.64)**	1.06	**25.49 (17.55-35.8)**
18 - 24	2.16	0.1	2.32 (0.63-5.94)	0.58	**14.13 (8.63 - 21.82)**
25 - 29	2.16	0.07	1.59 (0.19-5.75)	0.2	**4.74 (1.54 - 11.05)**
30 - 39	4.4[b]	0.18	**2.16 (1.12-3.78)**	0.16	1.91 (0.87 - 3.63)
40 - 49	4.4	0.06	0.72 (0.19-1.83)	0.32	**3.74 (2.22 - 5.92)**
50 - 64	4.4	0.1	1.23 (0.64-2.16)	0.19	**2.23 (1.34-3.48)**
≥65	4.4	0.04	0.5 (0.16-1.17)	0.08	0.91 (0.39-1.79)

*Background rates are rates per 100,000 persons per year.
**Reporting rates are per 100,000 doses of vaccine
[ł]Relative Risk (RR) is the reporting rate compared to the background rate when applied to the proportion of individuals vaccinated in each age group to July 1, 2021
[a]Gubernot et al, U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines
[b]Roth et al, Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019

Reviewer comment: Myocarditis and pericarditis emerged as a safety signal in VAERS and was jointly reviewed by FDA and CDC. Please see section 8.2 for further discussion of this safety signal.

Vaccine-associated enhanced disease (VAED):

There are not specific PTs for the important potential risk of vaccine-associated enhanced disease (VAED). Please see reviewer comments below regarding the VAERS search for PTs related to vaccine effectiveness.

Other:

Categories in the PVP that are considered “missing information” (i.e., use during pregnancy and lactation, vaccine effectiveness, and use in pediatric individuals <12 years of age), were also queried in VAERS. A VAERS search from December 11, 2020 (the date of authorization) to June 11, 2021 (run on June 22, 2021) for the System Organ Class (SOC) Pregnancy, Puerperium and Perinatal Conditions returned 1,050 reports, including 175 serious reports, 11 of which were deaths. Among the 11 death reports, eight involved a fetal (n=5) or infant death (n=3) and three were maternal deaths. The five fetal deaths were either miscarriage or intrauterine death that occurred less than two weeks post-maternal vaccination. The three infant deaths were: one death from thrombotic thrombocytopenic purpura (TTP) in a breastfed infant (symptom onset 1-day post-2nd-maternal vaccination), one report of premature birth 6-days post-vaccination with subsequent death (vaccine exposure during second trimester), and one report of premature birth at 21 weeks gestation with subsequent death 2-hours after birth (birth 13-days post-maternal vaccination and complicated by meconium aspiration and maternal chorioamnionitis due to a *Staphylococcus aureus* infection). The three maternal deaths were: a 32-year old female with asymptomatic Factor V Leiden who died 4-days after childbirth and 52-days post-vaccination (limited details); a 42-year old female with no reported PMH who died of a massive pulmonary embolus at 27-weeks gestation, and a 38-year old female with Type I diabetes mellitus, hemochromatosis, and sleep apnea who experienced maternal cardiac arrest with likely amniotic fluid embolism and disseminated intravascular coagulation (DIC) 14-days post-vaccination.

A separate query (run on July 13, 2021) of VAERS PT event counts for the SOC Pregnancy, Puerperium and Perinatal Conditions (from December 11, 2021 to June 11, 2021) showed a total of 1,589 PTs, including 546 PTs reported for serious reports and 21 PTs reported for deaths. Among serious reports, the top 10 most frequently reported PTs in the SOC Pregnancy, Puerperium and Perinatal Conditions were: exposure during pregnancy (n=189), abortion spontaneous (n=83), maternal exposure during pregnancy (n=40), fetal death (n=27), premature delivery (n=20), premature labor (n=17), delivery (n=15), induced labor (n=14), premature baby (n=11), and premature separation of placenta (n=9). Among death reports, PTs in the SOC Pregnancy, Puerperium and Perinatal Conditions reported more than once included exposure during pregnancy (n=4), maternal exposure during pregnancy (n=4), fetal death (n=4), spontaneous abortion (n=2), and premature baby (n=2).

Reviewer comment: Vaccine safety in pregnant women is being evaluated in a randomized controlled trial conducted by the sponsor, active surveillance studies conducted by the sponsor, and the CDC v-safe program. The background incidence of miscarriage varies by age and ranges from 10% in women aged 25-29 years up to 53% in women aged 45 years and older (Magnus, 2019). Review of the most common PTs reported in the SOC Pregnancy, Puerperium and Perinatal Conditions and individual review of VAERS death reports did not suggest patterns indicating a new safety concern that needs to be addressed in the PVP.

For “missing information” regarding vaccine effectiveness, VAERS was searched for the timeframe December 11, 2020 to June 11, 2021 (query run on June 17, 2021) using PTs for vaccination failure and drug ineffective. The search returned 1,788 reports that included the PT “vaccination failure” (n=254) and/or “drug ineffective” (n=1,565); 31 reports contained both PTs. Among the 254 reports including the PT vaccination failure, there were 24 serious reports and eight deaths. Among the eight deaths (three U.S. and five foreign reports), six were female and two were male; the median age was 71 years (range=37-98 years) and median onset as calculated by VAERS dates was 10 days post-vaccination (range=7-63 days). Most deaths occurred in individuals with reported underlying co-morbidities. Among the 1,565 reports of drug ineffective, there were 258 serious reports including 120 deaths. Among the 120 deaths, the majority (n=103, 86%) were foreign reports; 41 individuals were female, 57 were male, and 22 were of unknown sex; the median age was 84 years (range=17-99 years; 29 [24%] with unknown age) and median onset as calculated by VAERS dates was 4 days post-vaccination (range=0-26 days; 22 [18%] had incalculable VAERS dates). Most deaths occurred in individuals with reported underlying co-morbidities or unknown medical history.

Reviewer comment: There are VAERS reports of deaths due to COVID-19 in patients reported to be fully vaccinated. It is expected there may be some cases of vaccination failure, especially in elderly or immunocompromised subjects. Infection with a variant SARS-CoV-2 virus for which vaccination is less effective is also a possibility. Many reports concern elderly individuals with co-morbidities or contain limited details which makes complete assessment difficult. Generally, passive surveillance and spontaneous adverse event reporting cannot be used to draw conclusions regarding vaccine effectiveness due to the lack of a control group, reporter bias, and underreporting. Severe manifestations and death from COVID-19 raise the possibility of vaccine-associated enhanced disease (VAED), which has overlapping clinical manifestations with natural SARS-CoV-2 infection, making it difficult to differentiate VAED from severe COVID-19 disease in individual VAERS reports (Munoz, 2021). VAED is being assessed in a continuation of the Phase 3 clinical studies and active surveillance studies being conducted by the sponsor.

For “missing information” regarding individuals <12 years of age, VAERS was searched for the timeframe December 11, 2020 to June 11, 2021 (query run on June 22, 2021). There was a total of 273 reports in children <12 years of age, including 31 serious reports and two death reports. Among the 31 serious reports, the most commonly reported PTs (≥10%) were product administered to patient of inappropriate age (n=15), off-label use (n=11), headache (n=7), exposure via breast milk (n=5), rash (n=5), pyrexia (n=4), product use issue (i.e., product use in unapproved population; n=3), dizziness (n=3), nausea (n=3), and vaccination site pain (n=3). One death report concerned an 11-year-old female but it was not clear if she had received the vaccine or if she was exposed to other family members who received the vaccine; this report contained limited details and was difficult to interpret. The other death report concerned a 5-month-old breastfed infant who was diagnosed with TTP after the mother received

her 2nd Pfizer-BioNTech vaccine dose; symptom onset 1-day post-maternal vaccination (this report was included in the pregnancy and lactation review above).

Reviewer comment: The Pfizer-BioNTech COVID-19 vaccine is currently authorized for use in individuals age 12 years and older and the BLA has a proposed indication for use in individuals age 16 years and older. Review of VAERS data indicates that individuals younger than age 12 have received the product outside of clinical trials; no patterns of AEs were identified to suggest new safety concerns that warrant amendment to the PVP.

6.2 Data Mining Findings

Data mining of the VAERS database using Empirica Signal[1] with a data lock point of June 4, 2021, revealed the following PTs and subgroups had an increased disproportional reporting value (EB05≥2) for the Pfizer-BioNTech COVID-19 vaccine (Table 5):

Table 5: Preferred Terms with Disproportional Reporting in Empirica Signal for the Pfizer-BioNTech COVID-19 Vaccine

Preferred Term (PT)	US EB05	US Adult ≥65 years EB05	US Female EB05
Drug ineffective	1.964	2.034	1.779
Investigation	2.053	2.071	2.001
Product preparation issue	2.021	2.124	1.947
Weight	2.02	2.028	1.98

Reviewer comment: Reports with PT "drug ineffective" generally describe patients who contracted COVID-19 prior to being fully vaccinated or reports with limited details to assess timing or confirmation of COVID-19 infection or number of vaccine doses. Cases of vaccination failure might not always be reported to a spontaneous adverse event reporting system. Inferences that can be made from VAERS about COVID disease after vaccination are limited. Vaccine effectiveness is monitored through clinical trials, and post-authorization studies conducted by the sponsor. The PT "investigation" is non-specific and generally refers to investigations performed as part of work-up for signs or symptoms. The PT "product preparation issue" generally concerns reports with issues such as incorrect vaccine reconstitution or lack of reconstitution with diluent. The PT of

[1] Empirica Signal is a web-based platform that uses an automated approach to explore relationships in large datasets by generating statistical scores for combinations of products and events from drug or vaccine databases. Data mining is conducted to evaluate whether any events (i.e., MedDRA PTs) following use of a particular vaccine are disproportionally reported compared to all vaccine reports in VAERS; the threshold for signal detection is an EB05 value ≥2. (EBO5 is the lower bound of the 90% confidence limit for the Empirical Bayesian Geometric Mean). The data generated from Empirica Signal do not, by themselves, demonstrate causal associations, but the data might serve as a signal for further investigation and can be useful for hypothesis generation and exploration of potential concerns.

"weight" is non-specific and may refer to weight gain or loss in a patient or report of the patient's weight. Review of PTs with an EB05≥2 did not identify new safety concerns that need to be addressed in the PVP.

6.3 Discussion of U.S. Package Insert (USPI) Section 6.2 Post-marketing Experience

Sponsor proposed AEs for inclusion under Section 6.2 Post-marketing Experience include:

Cardiac Disorders: myocarditis and pericarditis

Gastrointestinal Disorders: diarrhea, vomiting

Immune System Disorders: severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions (e.g., rash, pruritis, urticaria, angioedema)

Musculoskeletal and Connective Tissue Disorders: pain in extremity (arm)

OBE/DE recommends inclusion of additional PTs to Section 6.2 Post-marketing Experience for:

- Dizziness
    - Among serious reports (as of August 2, 2021), dizziness ranks in the cumulative top 10 reported PTs with 11,107 events reported. A cumulative VAERS query for the PT dizziness, run on August 3, 2021, returned 35,104 reports (26,131 [74.4%] were U.S. reports), including 3,857 (11.0%) serious reports (145 of these were death reports). There were 26,032 (74.2%) reports concerning females and 8,615 (25.5%) concerning males; 457 (1.3%) reports did not include sex. The median onset based on VAERS dates=0 days (range=0-171 days post-vaccination) and median age=42 years (range=0.1-115 years).
- Dyspnea
    - Among serious reports (as of August 2, 2021), dyspnea ranks in the cumulative top 10 reported PTs with 10,506 events reported. A cumulative VAERS query for the PT dyspnea, run on August 3, 2021, returned 19,858 reports (12,757 [64.2%] were U.S. reports), including 6,235 (31.4%) serious reports (1,102 of these were death reports). There were 14,166 (71.3%) reports concerning females and 5,421 (27.3%) concerning males; 271 (1.4%) reports did not include sex. The median onset based on VAERS dates=0 days (range=0-207 days post-vaccination) and median age=48 years (range=0.1-109 years).

7 Pharmacovigilance Plan

7.1 Summary of Pharmacovigilance Plan

The sponsor submitted a PVP proposing routine pharmacovigilance (PV), including data capture aids (DCAs) for anaphylactic reactions and VAED, and post-authorization observational and active surveillance safety studies (Table 6). There are also ongoing clinical trials.

Table 6: Summary of Safety Concerns and Planned Pharmacovigilance Activities*

Safety Concern	Actions Proposed
Important Identified Risks	
Anaphylaxis	• Routine pharmacovigilance • Data capture aid • Communication of important identified risk via label (Sections 4 - *Contraindications*, 5.1 - *Management of Acute Allergic Reactions,* Section 6 - *Adverse reactions* - and 6.2 - *Post Authorization Experience*) • Completion of C4591001: Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 mRNA vaccine candidates against COVID-19 in healthy individuals • Three post-authorization safety studies to monitor safety of BNT162b2 (C4591009, C4591011, C4591012)
Myocarditis and Pericarditis	• Routine pharmacovigilance • Three post-authorization safety studies to monitor safety of BNT162b2 (C4591009, C4591011, C4591012) • FDA will also require a safety post-marketing study to further assess these serious risks
Important Potential Risks	
Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)	• Routine pharmacovigilance • Data capture aid • Completion of C4591001: Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 mRNA vaccine candidates against COVID-19 in healthy individuals • Four post-authorization safety studies to monitor safety of BNT162b2 (C4591008, C4591009,

	C4591011, C4591012)
Missing Information	
Use in pregnancy and lactation	• Routine pharmacovigilance • Completion of C4591015: A phase 2/3, placebo-controlled, randomized, observer blind study to evaluate the safety, tolerability, and immunogenicity of a SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older • Three post-authorization safety studies to monitor safety of BNT162b2 (C4591009, C4591011, C4591022 [Pregnancy Registry study])
Vaccine effectiveness	• Routine pharmacovigilance • Completion of BNT162-01 cohort 13 (Phase 1/2 dose-escalation clinical trial): Immunogenicity of Pfizer-BioNTech COVID-19 Vaccine in immunocompromised subjects, including assessment of antibody responses and cell-mediated responses • Three post-authorization vaccine effectiveness studies (C4591014: Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California • WI235284: determining RSV Burden and Outcomes in Pregnant Women and Older Adults Requiring Hospitalization. COVID-19 Amendment for COVID VE/ Sub-study 6 • WI255886: Avon Community Acquired Pneumonia Surveillance Study: A Pan- pandemic Acute Lower Respiratory Tract Disease Surveillance Study
Use in pediatric individuals <12 years of age	• Routine pharmacovigilance • Completion of C4591001 ≥12 to ≤15 years of age: Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 mRNA vaccine candidates against COVID-19 in healthy individuals. Randomized placebo-controlled study in 2,000 participants (1,000 active recipients) of 2 doses of BNT162b2 at a 21-day interval • Completion of C4591007 <12 years of age: Phase 1 open label dose-finding study to

	evaluate safety, tolerability, and immunogenicity and phase 2/3 placebo-controlled, observer-blinded safety, tolerability, and immunogenicity study of a SARS-CoV-2 mRNA vaccine candidate against COVID-19 in healthy children <12 years of age • One post-authorization safety study to monitor safety of BNT162b2 (C4591009)

*Adapted from sponsor's Pharmacovigilance Plan, Version 1.1 Table 46: Summary of Safety Concerns and Action Plans.

7.3 Summary of Post-authorization Safety Surveillance Studies

The sponsor proposes five post-authorization safety surveillance studies, which are summarized in the sections below. The sponsor also proposes three post-authorization vaccine effectiveness studies (C4591014, WI235284, WI255886):

- C4591014: Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California
- WI235284: Determining RSV Burden and Outcomes in Pregnant Women and Older Adults Requiring Hospitalization; COVID-19 Amendment for COVID VE/ Sub-study 6
- WI255886: Avon Community Acquired Pneumonia Surveillance Study: A Pan-pandemic Acute Lower Respiratory Tract Disease Surveillance Study

Reviewer comment: *The vaccine effectiveness study protocols were submitted to IND 19736/268 and are being reviewed by the CBER Biologics Effectiveness and Safety (BEST) team; see memorandums from CBER BEST team for study details and OBE assessment.*

7.3.1 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

The primary objective of this study is to estimate the real-world incidence of safety events of interest and other clinically significant events among U.S. healthcare workers vaccinated with the Pfizer-BioNTech COVID-19 vaccine following EUA. Secondary objectives are to evaluate whether the vaccine recipients experience increased risk of safety events of interest and other clinically significant events post-vaccination and to estimate the incidence rates of safety events of interest and other clinically significant events among sub-cohorts, such as individuals who are pregnant or immunocompromised, and stratified by age.

This prospective observational study will collect data based on participant self-report

(primarily using a secure web portal) at regular intervals for 24 months following vaccination. Events will be confirmed using medical records. This study aims to enroll at least 20,000 HCW who received a COVID-19 vaccine. Safety outcomes of interest area based on the priority list of AESI from the Brighton Collaboration's Safety Platform for Emergency Vaccines (SPEAC) Project (https://brightoncollaboration.us/priority-list-aesi-covid/; accessed 12/13/2020) and include the following (* denotes events that will only be collected if individual hospitalized):

- Neurologic: generalized convulsion/seizures, Guillain-Barré syndrome, aseptic meningitis, encephalitis/encephalomyelitis, other acute demyelinating diseases, transverse myelitis, multiple sclerosis, optic neuritis, Bell's palsy
- Immunologic: anaphylaxis, vasculitides*, arthritis/arthralgia, multisystem inflammatory syndrome (in adults), Kawasaki disease, fibromyalgia, autoimmune thyroiditis
- COVID-19: severe COVID-19 disease*, microangiopathy*, heart failure and cardiogenic shock*, stress cardiomyopathy*, coronary artery disease*, arrythmia*, deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, limb ischemia*, hemorrhagic disease*, acute kidney injury*, liver injury, Chillblain-like lesions, single organ cutaneous vasculitis*, erythema multiforme*
- Cardiac: myocarditis, pericarditis, acute myocardial infarction
- Hematologic: thrombocytopenia, disseminated intravascular coagulation
- Other: pregnancy outcomes, death, narcolepsy and cataplexy, non-anaphylactic allergic reactions

Data analysis will include descriptive statistics of vaccination and baseline characteristics, number and incidence rate for each safety event of interest will be calculated overall and within subgroups of interest. Qualitative comparisons will be made using hospitalization rates among non-vaccinated HCW enrolled in the HERO registry and external sources of background event rates. A self-matched comparative analysis will then be performed for events that appear to be associated with vaccination and that are amenable to self-matched analysis (e.g., adequate case counts, known risk interval).

The proposed study milestones are:

Interim report submission: June 30, 2021; December 31, 2021; June 30, 2022; December 31, 2022

Final study report submission: December 31, 2023

<u>Reviewer comment:</u> This study was proposed in the original EUA submission (EUA 27034/0) and the final study protocol was submitted to EUA 27034/68; OBE/DE reviewed the final study protocol and provided comments to the sponsor. In addition, the sponsor submitted an interim statistical analysis plan (SAP) and a protocol amendment (IND 19736/324) to expand the study population to include HCW families and community members, update recruitment strategies, and provide additional details

regarding the clinical event ascertainment process. The protocol amendment and SAP were reviewed by OBE/DE and are acceptable. Please see previous review memorandums for additional details.

7.3.2 C4591009: A non-interventional post-approval safety study of the Pfizer--BioNTech COVID-19 mRNA vaccine in the United States

The primary objective of this study is to estimate the relative risk (RR) or prevalence ratio of safety events of interest following receipt of at least one dose of the Pfizer-BioNTech COVID-19 vaccine in the overall study population and in pregnant women, in immunocompromised individuals, and in individuals with a history of COVID-19. Secondary objectives are to describe the proportion of individuals receiving at least one dose and a complete dose series, the timing and type of second dose of COVID-19 vaccine, and the baseline characteristics of individuals who receive at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared to those who do not receive any COVID-19 vaccine doses.

This is a retrospective cohort study comparing vaccinated individuals with concurrent unexposed comparators using claims and electronic health record data from partners in the Sentinel System. Safety events of interest will be aligned with events being monitored in the rapid cycle analysis of COVID-19 vaccines in the FDA's BEST system and CDC's VSD. The study will estimate incidence rates or incidence/prevalence proportions for each safety event of interest for matched exposed and unexposed cohorts; comparative analyses will also estimate hazard ratios or incidence rate ratios and 95% CI within propensity score-matched cohorts. Individuals of all ages will be included in the descriptive analysis of vaccine utilization while the safety analysis will be limited to individuals within the age-indicated population for the Pfizer-BioNTech COVID-19 vaccine. The study period will extend a minimum of three years post-EUA.

The proposed study milestones are:

Final protocol submission: August 31, 2021

Monitoring report submission: October 31, 2022

Interim report submission: October 31, 2023

Final study report submission: October 31, 2025

<u>Reviewer comment:</u> This study was proposed in the EUA submission to expand the Pfizer-BioNTech COVID-19 vaccine indication to pediatric individuals age 12-15 years (EUA 27034/132); a study protocol synopsis was submitted with the BLA.

7.3.3 C4591011: Active safety surveillance of the Pfizer-BioNTech COVID-19 vaccine in the U.S. Department of Defense population following Emergency Use Authorization

The primary objective of this study is to assess whether individuals and sub-cohorts of interest (i.e., pregnant women, immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 vaccine, and individuals with prior SARS-CoV-2 infection) in the Department of Defense (DoD) military health system (MHS) experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine. Secondary objectives are to characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the DoD MHS.

This active safety surveillance study will utilize a rapid-cycle, longitudinal, observational cohort study design to assess real-world safety of the Pfizer-BioNTech COVID-19 vaccine using a self-controlled risk interval design and a cohort design with two comparator populations (2018/2019 season influenza vaccine recipients and unvaccinated matched controls). Safety events of interest are aligned with AESIs from the Brighton Collaboration's SPEAC Project, FDA, and CDC's Advisory Committee on Immunization Practices (ACIP) enhanced safety monitoring recommendations. A stepwise data analysis process will include signal detection, evaluation, and verification. The study will use coding and medical record data from the DoD MHS Data Repository and will be conducted for 30-months post-EUA.

The proposed study milestones are:

Interim report submissions: June 30, 2021; December 31, 2021; June 30, 2022; December 31, 2022

Final study report submission: December 31, 2023

Reviewer comment: This study was proposed in the original EUA submission (EUA 27034/0). The final study protocol was submitted to EUA 27034/68 and reviewed by the CBER BEST team. An IR response (EUA 27034/186) indicated that the start date for C4591011 is delayed due to a change in study collaborators and the first interim report will be submitted by December 31, 2021 rather than June 30, 2021. Please see previous review memorandums for additional details.

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

The primary objective of this study is to assess whether individuals and sub-cohorts of interest (i.e., immunocompromised, elderly, individuals with specific comorbidities, individuals receiving only one dose of the Pfizer-BioNTech COVID-19 vaccine, and individuals with prior SARS-CoV-2 infection) in the Veterans Health Administration

(VHA) system experience increased risk of safety events of interest following receipt of the Pfizer-BioNTech COVID-19 vaccine. Secondary objectives are to characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA.

This active safety surveillance study will utilize a rapid-cycle, longitudinal, observational cohort study design to assess real-world safety of the Pfizer-BioNTech COVID-19 vaccine using a self-controlled risk interval design and an active comparator design (2014/2015 through 2018/2019 seasonal influenza vaccine recipients). Safety events of interest are aligned with AESIs from the Brighton Collaboration's SPEAC Project, FDA, and CDC's ACIP enhanced safety monitoring recommendations. A stepwise data analysis process will include signal detection, evaluation, and verification. The study will use coding and medical record data from the VHA Corporate Data Warehouse which is an integrated electronic medical record system and will be conducted for 30-months post-EUA.

The proposed study milestones are:

Interim report submissions: June 30, 2021; December 31, 2021; June 30, 2022; December 31, 2022

Final study report submission: December 31, 2023

Reviewer comment: This study was proposed in the original EUA submission (EUA 27034/0). The final study protocol was submitted to EUA 27034/68 and reviewed by the CBER BEST team. An IR response (EUA 27034/186) indicates that the protocol will be revised to incorporate CBER BEST team comments regarding the addition of a contemporary unvaccinated comparator cohort for signal evaluation; a revised protocol will be submitted by August 31, 2021. Please see previous review memorandums for additional details.

7.3.5 C4591022: Pfizer-BioNTech COVID-19 Vaccine exposure during pregnancy: A non-interventional post-approval safety study of pregnancy and infant outcomes in the Organization of Teratology Information Specialists (OTIS)/Mother To Baby Pregnancy Registry

The primary objective of this pregnancy registry study is to assess whether pregnant women in the Organization of Teratology Information Specialists (OTIS) Pregnancy Registry receiving the Pfizer-BioNTech COVID-19 vaccine experience increased risk of pregnancy and infant safety outcomes. The secondary objective is to characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among pregnant women in the OTIS registry.

This prospective, observational cohort pregnancy registry study will utilize two comparator groups: 1) pregnant women who received an influenza or Tdap (tetanus, diphtheria, and acellular pertussis) vaccine during pregnancy and 2) pregnant women who received no vaccines during pregnancy. The study aims to enroll 1800 pregnant women over a 3-year recruitment period. Pregnancy and infant safety outcomes will include major congenital malformations, spontaneous abortion, stillbirth, preterm

delivery, small for gestational age, and small for age postnatal growth to one year of age. Data will be collected using maternal interviews, medical record review, and a pregnancy exposure diary. Data analysis will include descriptive statistics, birth prevalence rates and incidence rates, and risk estimates.

The proposed study milestones are:

Final protocol submission: July 1, 2021

Interim report submissions: January 31, 2022; January 31, 2023; January 31, 2024; January 31, 2025

End of data collection: December 31, 2024

Final study report submission: December 1, 2025

Reviewer comment: This pregnancy registry study will be a post-marketing commitment (PMC).

8 DE Assessment of Sponsor's Pharmacovigilance Plan

8.1 Important Identified Risk: Anaphylaxis

The risk of anaphylaxis was recognized early in the post-authorization time period and information was added to the EUA Fact Sheets for healthcare providers and recipients and caregivers. One BNT162b2-related-SAE of anaphylactoid reaction occurred in a clinical trial (C4591001) participant who originally received placebo and then received BNT162b2 after unblinding. This individual had an ongoing medical history of drug hypersensitivity and food and seasonal allergies and had onset 2-days post-1st dose of BNT162b2; she self-administered an epinephrine pen and symptoms resolved the same day. In addition, the sponsor's summary of post-authorization AE reports identified 1,002 cases of anaphylaxis that met the Brighton Collaboration (BC) definition level 1 (highest level of certainty) through 4 (reported event with insufficient evidence to meet case definition), including nine fatal events. A VAERS search for reports of anaphylaxis returned 1,034 reports, including 524 serious reports and 12 death reports; there were no patterns suggestive of any new safety signals.

The important identified risk of anaphylaxis, which can be fatal or life-threatening, will be monitored through routine pharmacovigilance activities, including a data capture aid to identify relevant clinical information, and post-authorization safety studies. This safety concern has labeling proposed in the following sections of the USPI:

- Section 4 Contraindications
- Section 5 Warnings and Precautions, 5.1 Management of Acute Allergic Reactions
- Section 6 Adverse Reactions

Reviewer comment: The proposed PVP is adequate to monitor the risk of anaphylaxis.

8.2 Important Identified Risk: Myopericarditis and Pericarditis

During the post-authorization period, myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine was reported to VAERS. Myocarditis and pericarditis emerged as a safety signal in VAERS, and there are ongoing analyses for further characterization of these risks. CDC issued clinical considerations regarding myocarditis and pericarditis after receipt of mRNA COVID-19 vaccines among adolescents and young adults in May 2021. Myocarditis and pericarditis following mRNA COVID-19 vaccines was discussed at the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) and CDC Advisory Committee on Immunization Practices (ACIP) meetings in June 2021. The EUA Fact Sheet was revised on June 25, 2021 to add a Warning for myocarditis and pericarditis and the PVP was amended to include myocarditis and pericarditis as important identified risks. The sponsor's PVP indicates that a mechanism of action has not been established for how the vaccine could cause myocarditis and pericarditis, however potential hypotheses are related to an immune stimulated response, a general systemic inflammatory response, or a hypersensitivity response. The revised PVP (Version 1.1) also included post-authorization data for myocarditis and pericarditis among individuals 16 years of age and older through June 18, 2021. As per the sponsor, there was a total of 823 reports, including 490 reports of myocarditis and 372 reports of pericarditis. A VAERS search for reports of myopericarditis returned 1,023 reports (1,012 were U.S. reports), including 809 serious reports (seven were death reports concerning six unique individuals). As described in the O/E analysis, given a 7-day risk window (Tables 3 and 4), the reporting rate and RR is elevated in age groups under 30 years, with more cases occurring after dose 2. The reporting rate and RR was higher among males than females for almost all age groups.

Monitoring for myocarditis and pericarditis is ongoing and includes the following activities:

- Continued passive surveillance using VAERS
- Vaccine Safety Datalink (VSD) analyses for safety signals
- Ongoing Sponsor passive surveillance using worldwide adverse events data
- Ongoing Sponsor active surveillance studies

In addition, a safety post-marketing requirement (PMR) under FDAAA is warranted to further characterize the serious risk of myopericarditis.

This safety concern has labeling proposed in the following sections of the USPI:

- Section 5 Warnings and Precautions
- Section 6 Adverse Reactions

<u>Reviewer comment:</u> The sponsor's proposed PVP and FDA required post-marketing study is adequate to monitor and further assess the risk of myocarditis and pericarditis including long-term follow up. Please see PVP addendum memo for review of the safety PMR.

8.3 Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Vaccine-associated enhanced disease (VAED) is a modified and/or severe presentation of an infectious disease in individuals exposed to a wild-type pathogen following receipt of a vaccine designed to prevent infection (Munoz, 2021). The clinical manifestations of VAED are within the spectrum of natural disease and are difficult to separate from vaccine failure; there are no specific biomarkers or histopathologic findings for VAED (Munoz, 2021). In addition, there can be multiple pathophysiologic pathways that could lead to VAED/VAERD in general, such as immune complex mediated enhanced disease, cellular immunity in enhanced respiratory disease, antibody mediated enhanced disease, cytokine activation, or vaccine-induced enhancement of infection acquisition (Munoz, 2021). The sponsor cites VAED as a theoretical risk based on animal models of related betacoronaviruses, including SARS-CoV-1 and MERS-CoV, and disease enhancement that was seen in vaccinated children following infection with natural virus after receipt of inactivated respiratory syncytial virus vaccine. Data from the blinded placebo-controlled follow-up period in Study C4591001 show one confirmed case of post-vaccination severe COVID-19 compared to 31 confirmed cases in the placebo group. No post-authorization AE reports have been identified as cases of VAED/VAERD. The important potential risk of VAED will be monitored through routine pharmacovigilance activities, including a data capture aid to identify relevant clinical information, and post-authorization safety studies.

Reviewer comment: The favorable balance of confirmed cases of severe COVID-19 in BNT162b2 vs placebo recipients in Study C4591001 is reassuring. The proposed PVP is adequate to monitor the potential risk of VAED and VAERD.

8.4 Missing Information: Use in pregnancy and lactation

Pregnant women were excluded from the pivotal clinical trial and the safety profile of the Pfizer-BioNTech COVID-19 vaccine in pregnant or lactating women is not known. Post-authorization data from the sponsor's safety database and a VAERS search did not identify any patterns suggesting new safety concerns. Missing information regarding the use of the product during pregnancy and lactation will be monitored through routine pharmacovigilance activities, a clinical trial, and post-authorization safety studies, including a Pregnancy Registry study which will be a PMC. The lack of safety data will be communicated in product labeling (Section 8.1 Pregnancy and 8.3 Lactation).

Reviewer comment: The proposed PVP is adequate to monitor for use in pregnancy and lactation.

8.5 Missing Information: Vaccine effectiveness

Real-world vaccine effectiveness of the Pfizer-BioNTech COVID-19 vaccine outside of clinical trials and in larger and more diverse populations is not known. Post-

authorization data from the sponsor's safety database identified 16 cases of vaccination failure out of 42,086 total AE cases reported cumulatively to February 28, 2021. The sponsor's review of these cases did not reveal any new safety signals associated with the lack of vaccine effectiveness. In addition, a VAERS search returned 1,788 reports that included the PT vaccination failure (n=254) and/or drug ineffective (n=1,565); 31 reports contained both PTs; there were no patterns suggestive of any safety signals. Missing information regarding real-world vaccine effectiveness will be monitored through routine pharmacovigilance activities and post-authorization real-world vaccine effectiveness studies. Data on vaccine efficacy in clinical trials will be communicated in product labeling (Section 14 Clinical Studies).

Reviewer comment: The proposed PVP is adequate to monitor vaccine effectiveness.

8.6 Missing Information: Use in pediatric individuals <12 years of age

Pediatric individuals <12 years of age were excluded from the pivotal clinical trial and the safety profile in this population is not known. Post-authorization data from the sponsor's safety database revealed 34 cases concerning 132 AEs; review of PTs did not reveal new safety concerns. A VAERS search returned 273 reports concerning individuals <12 years of age and did not suggest any patterns concerning for any new safety signals. Missing information regarding pediatric individuals <12 years of age will be monitored through routine pharmacovigilance activities and a post-authorization safety study. There are also ongoing clinical trials. The lack of safety data will be communicated in product labeling (Section 8.4 Pediatric Use).

Reviewer comment: The proposed PVP is adequate to monitor use in individuals <12 years of age.

9 DE Conclusions

Based on review of available data, there is a new safety signal for myopericarditis from post-authorization safety surveillance which warrants a FDAAA Title IX PMR safety study to assess the important identified risk of myopericarditis. Please see PVP addendum memo for review of the safety PMR. The sponsor's proposed Pregnancy Registry study (C4591022) will be a PMC. In addition, the safety of BNT162b2 can be monitored through routine PV activities, risk communication through labeling, and the additional post-authorization safety studies proposed by the sponsor.

10 DE Recommendations

Should the product be approved, based on the review of the clinical trial safety data, and the post-authorization safety data, OBE/DE recommends the following actions:

- **Routine pharmacovigilance** in accordance with adverse event reporting regulations under 21 CFR 600.80, as per the sponsor's proposed PVP.

- **Post-marketing requirement (PMR) safety study** under Section 505(o) of the FDCA (amended by FDAAA, Title IX, Section 901), to assess the serious risk of myopericarditis. (Please see PVP addendum memo for review of the safety PMR.)
- **Post-marketing commitment (PMC) safety study** for a pregnancy registry (C4591022) to assess whether pregnant women receiving the Pfizer-BioNTech COVID-19 vaccine experience an increased risk of pregnancy and infant safety outcomes compared to two comparator groups.
- **Voluntary post-marketing studies**: Post-EUA studies that continue as voluntary studies will be followed through updates in periodic safety update reports (PSURs).

OBE/DE also recommends inclusion of the following AEs to the USPI, Section 6.2 Post-marketing Experience: dizziness and dyspnea.

At this time, the available safety data do not suggest a safety concern that would require a REMS. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

11 References

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

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

Gubernot D, Jazwa A, Niu M, Baumblatt J, U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021 Jun 23;39(28):3666-3677. PMID: 34088506.

Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Haberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. BMJ. 2019;364:l869.

Munoz FM, Cramer JP, Dekker CL, Dudley MZ, Graham BS, Gurwith M, Law B, Perlman S, Polack FP, Spergel JM, Van Braeckel E, Ward BJ, Didierlaurent AM, Lambert PH; Brighton Collaboration Vaccine-associated Enhanced Disease Working Group. Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2021 May 21;39(22):3053-3066. doi: 10.1016/j.vaccine.2021.01.055. Epub 2021 Feb 23. PMID: 33637387; PMCID: PMC7901381.

Myocarditis Brighton Collaboration Definition (Pandemic Emergency Response Process_Draft Release), Version 1.4.2; May 30, 2021. Available at: https://brightoncollaboration.us/wp-content/uploads/2021/07/Myocarditis-CD_Version_1.4.2_30.May_.2021__LOC_ALL__FINAL.POSTING.pdf

Roth, G. A., Mensah, G., Johnson, C.O., Addolorato, G., Journal of the American College of Cardiology J Am Coll Cardiol. 2020 Dec 22; 76(25): 2982–3021. PMID: 33309175.

Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, de Souza Brito G, Heininger U, Imoukhuede B, Khamesipour A, Erlewyn-Lajeunesse M, Martin S, Mäkelä M, Nell P, Pool V, Simpson N; Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5675-84. doi: 10.1016/j.vaccine.2007.02.064. Epub 2007 Mar 12. PMID: 17448577.

Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. JAMA. 2021 Mar 16;325(11):1101-1102. doi: 10.1001/jama.2021.1967. PMID: 33576785