Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

CBER SENTINEL PROGRAM SUFFICIENCY MEMORANDUM

From:	Joyce Obidi Health Scientist, CBER Surveillance Program Office of Biostatistics and Epidemiology (OBE)
Through:	Hui-Lee Wong Associate Director, CBER Surveillance Program, OBE
Subject:	CBER Sentinel Program Sufficiency Assessment
Product:	COMIRNATY; BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine)
Sponsor:	Pfizer
STN:	125742/0
Proposed Indication:	Active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals ≥16 years of age.
Approval Type:	☒ Priority ☐ Standard review
Submission Date:	May 18, 2021
Action Due Date:	January 16, 2022

1. Objectives/Scope:

This memo reviews the capability and sufficiency of the CBER active post-market risk identification and analysis system referred to as the CBER Sentinel Program to evaluate the serious risk for myocarditis and pericarditis following receipt of BNT162b2, a COVID-19 Vaccine indicated for active immunization to prevent COVID-19 disease caused by SARS-CoV-2 in individuals ≥16 years of age in lieu of a safety post-market requirement (PMR) study under FDAAA[1]. The CBER Sentinel Program covers activities conducted through the contract with the Harvard Pilgrim Health Care Institute, the current and future contracts through the Biologics Effectiveness and Safety (BEST) Initiative, and the interagency agreement with the Centers for Medicare and Medicaid (CMS). Please see the STN 125742/0 OBE/Division of Epidemiology (DE) review of the Pharmacovigilance Plan (PVP) for background on the serious risks of myocarditis and pericarditis, and subclinical myocarditis. Post-authorization safety data identified serious risks for myocarditis and pericarditis after COMIRNATY, with increased risk in males under 30 years of age, particularly following the second dose, and onset of symptoms within 7 days following vaccination. At the end of May 2021 CDC issued clinical considerations regarding myocarditis and pericarditis after receipt of mRNA COVID-19 vaccines among adolescents and young adults (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html). The topic was presented and discussed at the FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting on June 10, 2021 and the Advisory Committee for Immunization Practices (ACIP) meeting on June 23, 2021. The Emergency Use Authorization (EUA) Fact Sheet was revised on June 25, 2021 to add a Warning for myocarditis and pericarditis. A postmarketing observational safety study(ies) is needed to assess myocarditis and pericarditis following administration of COMIRNATY (BNT162b2) to:

a. Quantify the magnitude of risk by age, sex, and dose
b. Follow up cases for recovery status and long-term sequelae
c. Characterize subclinical cases of myocarditis

2. CBER Sentinel Program Sufficiency Assessment:

Determination of the sufficiency of the CBER Sentinel Program to further characterize the serious risk of myocarditis and pericarditis with BNT162b2 was based on the following factors:

[1] Under section 901 of the Food and Drug Administration Amendments Act (FDAAA), *"The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B)."*NOTE: The active post-market risk identification and analysis system under subsection (k)(3) refers to the Sentinel program.

[2] ISBT 128 is a global standard for the safe identification, accurate labeling, and efficient information transfer of medical products of human origin (including blood, cells, tissues, milk, and organ products) across disparate national and international health care systems. https://www.iccbba.org/isbt-128-basics

2.1 Identification of exposure to BNT162b2

2.2 Identification of the appropriate study population: Patients ≥ 16 years of age

2.3 Characterization of occurrence of myocarditis and pericarditis, and subclinical myocarditis, with BNT162b2

2.4 Identification of exposure to comparator product (when applicable)

2.1 Assessment for identification of exposure to BNT162b2

2.1.1. Is the CBER Sentinel Program able to identify the product (exposure) of interest?

Please answer each question i – xi, including sub-questions.		Yes	No
i.	Is this the first or the only FDA-approved product for the indication?	☒	☐
ii.	Can the exposure be identified using a billing or reimbursement coding system? *If yes, check all that apply:* ☒ *CPT* ☒ *HCPCS* ☒ *NDC* ☐ *ICD* ☐ *Other: [Coding system]*	☒	☐
iii.	Is the ISBT 128 coding system[2] needed for the product identification?	☐	☒
iv.	Can the reimbursement code of the product identify the brand name?	☒	☐
v.	Is a history of uptake for previously approved products for the same indication needed? *If yes, list all products:*	☐	☒
vi.	Is medical chart review needed to identify or validate the identification of this product?	☐	☒
vii.	Are claims data sources needed for exposure identification?	☒	☐
viii.	Are electronic health record (EHR) data sources needed for exposure identification?	☐	☒
ix.	Are any other health record type data sources needed for exposure identification? *If yes, all health record types needed: [e.g., Registries, any other health records]*	☒	☐
x.	Is product lot number needed for identification of this product?	☐	☐
xi.	Is there a care setting of interest required for identification of this product? *If yes, check all that apply:* ☐ *Inpatient* ☐ *Outpatient* ☐ *Emergency Room* ☐ *Other: Hospitalization*	☐	☒

2.1.2. Summary for product exposure identification

☒ Available data sources in the CBER Sentinel Program are *sufficient to identify the exposure of the product* BNT162b2 *due to reasons identified in* 2.1.1.ii. Billing codes for BNT162b2 allows for clear ascertainment of exposure to the product.

☐ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the exposure of the product [name]* due to reasons identified in [list all bullets from 2.1.1.i.—2.1.1.xi. that support insufficiency].

2.2. Assessment for identification of the appropriate study population: Patients ≥ 16 years of age

2.2.1. Is the CBER Sentinel Program able to identify the study population of interest?

Please provide an answer for each question i – vi, including sub-questions.		**Yes**	**No**
i.	Does age need to be identified? *If yes, list the inclusion and exclusion criteria.. Check all that apply for the level of granularity in ☐ Days ☐ Months ☒ Years*	☒	☐
ii.	Does sex need to be identified? *If yes, list the inclusion [List the sex to be included] and exclusion criteria [List the sex to be excluded].*	☐	☒
iii.	Does race need to be identified? *If yes, list the inclusion [List race to be included] and exclusion criteria [List race to be excluded]*	☐	☒
iv.	Can the study population be identified in the data sources required for the exposure and outcome identification?	☒	☐
v.	Was this population previously identified within the CBER Sentinel Program activities?	☒	☐
vi.	Is there a requirement for linking mothers to their newborns in the data sources?	☐	☒

2.2.2. Summary for identification of study population

☒ Available data sources in the CBER Sentinel Program are *sufficient to identify the study population of interest*, patients > 16 years of age, due to reasons identified in 2.2.1.i - 2.2.1.vi. This study population of interest has been identified in the data sources required of exposure (BNT162b2) and outcome (myocarditis/pericarditis).

☐ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the study population of interest* due to reasons identified in [list all bullets from 2.2.1.i.—2.2.1.vi. that support insufficiency].

2.3 Assessment for characterization of occurrence of myocarditis and pericarditis, and subclinical myocarditis

2.3.1 Is the CBER Sentinel Program able to identify the outcome(s) of interest?

Please provide an answer for each question i – xi, including sub-questions.		Yes	No
i.	Can the outcome of interest be identified using a billing or reimbursement coding system? If *yes, check all that apply: ☒ ICD ☐ CPT ☐ Other: Medical Record Review*	☒	☐
ii.	Are there surrogate data elements or biomarkers that can assist to identify the outcome of interest? *If yes, check all that apply: ☐ Laboratory Test Results ☐ Prescription drug ☐ Order of lab test ☐ Order of other diagnostic modalities ☐ Other: [Data element/Biomarker]*	☐	☒
iii.	Are there specific care settings in which this outcome is identified? *If yes, check all that apply: ☒ Inpatient ☒ Outpatient ☒ Emergency Room ☒ Other: Hospitalization*	☒	☐
iv.	Was this outcome previously identified within the CBER Sentinel Program activities? *If yes, in what population was it used? It was used in a similar population of Medicare beneficiaries 65y and older.*	☒	☐
v.	Is there a validated and acceptable algorithm available in the literature to identify the outcome of interest? *If yes, list the PPV [PPV] and describe the population in which it was validated:*	☐	☒
vi.	Is a minimum follow-up time needed to identify the outcome of interest? *If yes, what is the required follow-up period? 3-6 months*	☒	☐
vii.	Is medical chart review required to identify or validate the identification of the outcome?	☒	☐
viii.	Is the prevalence of the outcome known? *If yes, list background rates. 0.95-2/16 per 100,000 PY in Gubernot 2021*	☒	☐
ix.	Are claims data sources needed for outcome characterization?	☒	☐
x.	Are electronic health record (EHR) data sources needed for outcome characterization?	☒	☐
xi.	Are any other health record type data sources needed for outcome characterization? *If yes, all health record types needed: Registries*	☒	☐

2.3.2 Summary of outcome characterization

☒ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the outcomes of* myocarditis and pericarditis due to reasons identified in 2.3.1.vi.—2.3.1.viii. Based on the prevalence of background rates estimated in the CBER Sentinel data sources and the number of observed myocarditis/pericarditis events in the CBER Sentinel Program on-going near-real time surveillance, the CBER Sentinel data sources are currently not sufficiently powered to assess the magnitude of risk for the 12-30 years old that has been reported in VAERS in an epidemiology study (e.g., self-controlled analyses). CBER Sentinel will continue to monitor these safety outcomes. In order to follow up cases for recovery status and long-term sequelae, a minimum follow up time of 3-6 months is required. CBER Sentinel data sources do not have sufficient longitudinal data on patients to conduct this type of analysis. Additionally, a study of subclinical myocarditis using CBER Sentinel data sources is not feasible because of the absence of a definition of subclinical myocarditis and unknown background incidence of troponin abnormalities.

2.4. Assessment for identification of exposure to comparator product (when applicable): NOT APPLICABLE

2.4.1. Is the CBER Sentinel Program able to identify the required comparator product?

Respond to the questions below, if applicable.

Please provide an answer for each question i – xi, including sub-questions		Yes	No
i.	Is a comparator product needed for the assessment? ***If no, skip to section III for Recommendation***. *If yes, list all products:*	☐	☐
ii.	Can the comparator product be identified using a billing reimbursement code? *If yes, check all that apply: ☐CPT ☐HCPCS ☐NDC ☐ICD ☐Other:[Billing reimbursement code]*	☐	☐
iii.	Can the comparator product be exclusively identified using the billing reimbursement codes?	☐	☐
iv.	Is the ISBT 128 coding system[2] needed for the comparator product identification?	☐	☐
v.	Can the reimbursement code of the comparator product identify the brand name?	☐	☐
vi.	Is medical chart review needed to identify or validate the identification of this comparator product?	☐	☐
vii.	Are claims data sources needed for exposure identification of the comparator product?	☐	☐
viii.	Are electronic health record (EHR) data sources needed for exposure identification of the comparator product?	☐	☐

Please provide an answer for each question i – xi, including sub-questions		Yes	No
ix.	Are any other health record type data sources needed for exposure identification of the comparator product? *If yes, list all health record types needed: [e.g., Registries, any other health records]*	☐	☐
x.	Is product lot number needed for identification of this comparator product?	☐	☐
xi.	Is there a care setting of interest for identification of this comparator product? *If yes, check all that apply:☐ Inpatient ☐ Outpatient ☐ Emergency Room ☐ Other: Hospitalization*	☐	☐

2.4.2. Summary for comparator exposure identification

☐ Available data sources in the CBER Sentinel Program are *sufficient to identify the comparator product* due to reasons identified in [list all bullets from 2.4.1.i.—2.4.1.xi. that support sufficiency].

☐ Available data sources in the CBER Sentinel Program are *NOT sufficient to identify the comparator product* due to reasons identified in [list all bullets from 2.4.1.i.—2.4.1.xi. that support insufficiency].

3. Recommendation:

☐ The CBER Sentinel Program is *sufficient* to assess the serious risk of [describe] associated with [product] at this time. [Summarize all bullets 2.1.—2.4. that support sufficiency]

☒ The CBER Sentinel Program is NOT sufficient to assess the serious risks of myocarditis and pericarditis, and subclinical myocarditis associated with COMIRNATY (BNT162b2) in lieu of PMR safety studies under FDAAA. At the time of BLA approval, the data sources in the CBER Sentinel Program are not sufficient to identify the outcomes due to lack of sufficient power to assess the magnitude of risk in patients 12-30 years of age. In addition, CBER Sentinel Program is not sufficient to follow up cases for recovery status and long-term sequelae, or for identification and characterization of subclinical myocarditis cases.