Center for Biologics
Evaluation and Research

CENTER DIRECTOR DECISIONAL MEMO

August 25, 2025

sBLA:	STN 125742/696 and STN 125742/656
Product Name:	COMIRNATY
Indication:	Indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in adults 65 years of age and older and individuals 5 through 64 years who have at least one underlying condition that puts them at high risk for severe outcomes from COVID-19
Applicant:	Pfizer BioNTech
Author:	Vinayak Prasad, MD, MPH, Director, Center for Biologics Evaluation and Research (CBER), FDA

Summary:

This memorandum explains CBER OCD's decision on the above submission. I have read the reviews and recommendations of the BLA review team. In addition to those, I have read and reviewed pertinent portions of the sponsor's submission, as well as research on this topic in the peer reviewed literature.

The review team has done a commendable job in summarizing and analyzing the submission to date. Nevertheless, I disagree with certain aspects of their conclusions and instead reach the conclusion described below.

The decision to approve the Supplemental Biologics License Application (sBLA) for COMIRNATY is for the following indication: for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 65 years of age and older and individuals 5 through 64 years who have at least one underlying condition that puts them at high risk for severe outcomes from COVID-19. Moreover, the company has agreed to at least 3 postmarketing commitments (PMCs):

> Study 1: Prospectively designed study to evaluate safety and immunogenicity of COMIRNATY (2025-2026 Formula) in participants 65 years of age and older and 12 years through 64 years of age with at least one underlying condition that puts them at high risk for severe outcomes from

COVID-19. Please note that the study should be adequately powered for prespecified hypothesis testing of study immunogenicity endpoints for each age group in which COMIRNATY is approved for use.

Study 2: A randomized, double-blind, saline placebo-controlled study to evaluate the efficacy and safety of COMIRNATY in individuals 50 through 64 years of age without underlying condition that puts them at high risk for severe outcomes from COVID-19.

Study 3: Prospectively designed study to evaluate safety and immunogenicity of COMIRNATY (2025-2026 Formula) in participants: 5 years through 11 years of age with at least one underlying condition that puts them at high risk for severe outcomes from COVID- 19.

Additionally, at the time of this writing, CBER is working to negotiate with the sponsor a substudy of study 2 with a focus on measuring circulating spike protein and symptoms of long-covid and/or the post-acute covid-19 syndrome.

Summary Discussion:

The manufacturer's application forces FDA CBER to confront the question: is there substantial certainty of a net clinical benefit (benefits outweigh harms) to vaccinating healthy persons with this mRNA vaccine? CBER's answer is, at the present time, with best available information, no. At the same time, CBER's answer for persons with risk factors is: yes.

First, consider that COVID-19 severe disease, hospitalization and death have fallen since initial years of the pandemic. These rates are lower in healthy persons than people with risk factors. Notably, the Applicant has agreed to a revised indication that focuses on people with risk factors and CBER has granted this approval.

Second, observational studies and case control studies used to infer vaccine effectiveness have methodologic limitations. Specifically, families who choose to vaccinate kids and healthy people who choose to receive vaccination are fundamentally different than those who don't, and we cannot easily separate the treatment effect from those underlying differences. Case control studies hinge on the fact that cases and controls are sampled from the same underlying population, and this assumption is often incorrect.

Third, the Applicant has not shown that COVID-19 vaccination reduces Long COVID or transmission in any setting at any age with high quality data. Neither has the applicant nor a third party shown fewer missed days of school or work with high quality data. These endpoints cannot be considered for regulatory purposes. The FDA primary review teams have never allowed any company to make these claims about any COVID-19 vaccine, including for the Applicant.

Fourth, several of the studies the Applicant has submitted occurred in a COVID-19 landscape much different than the present day. Whether these studies retain relevance with wider population immunity and mutational changes to the virus is debated. One important factor in vaccinating healthy persons is the fraction who were previously exposed to the virus through normal life. The potential upper bound absolute benefit to a person who has had and recovered from COVID-19, and one who has done so recently, is lower than one that has not been exposed to the virus.

Fifth, although COVID-19 vaccines have been given to billions of individuals and the harms have been studied in depth, no one knows if these products have harms that only materialize 10 or 20 years later, as such is a necessary limit of time. It is ignorant to claim that unknown long-term risks are not possible.

Sixth, much of the Applicant's submission concerns immunogenicity or the body's ability to make antibodies that neutralize the virus. Make no mistake—antibody titers are a surrogate endpoint. They can and do correlate with improved clinical outcomes in some, but not all circumstances. One cannot be certain of net-clinical benefit merely because antibodies are increased; this is not gold standard science. The human body does not actively manufacture all antibodies it is capable of producing at all times. Instead, it mobilizes antibody production from memory cells when appropriate. Vaccine doses can increase antibodies, but fail to further improve clinical outcomes. The proper interpretation of surrogate endpoints is key to understanding this application. CBER has shown flexibility and will accept these surrogate endpoints for children at high risk of severe COVID-19 outcomes, but will not for healthy people. This is also why CBER will limit language about concurrent administration of vaccines.

Seventh, CBER's risk-based regulatory philosophy to COVID-19 vaccination is no secret, has been announced publicly, and discussed widely. The CBER OCD and FDA Commissioner have published the framework in the *New England Journal of Medicine* (further discussed below), which broadly holds that vaccines for COVID-19 will be made available for elderly individuals (>65 years old) and younger individuals with risk factors for severe COVID-19 based on immunogenicity data, but that randomized trials measuring clinical outcomes will be required to approve these products for healthy individuals.

Eighth, although not a consideration in CBER's decision making, CBER notes that the majority of peer European nations no longer advises healthy persons to undergo COVID-19 vaccination, and the US has been a global outlier with its annual boosters for all in perpetuity strategy.

FDA has a statutory mandate to only approve products when we have substantial certainty benefits outweigh harms and, in cases when we do not, sponsors are free to prove to the agency and the American people the worth of their products with randomized trials. We do not have substantial certainty benefits outweigh risks for healthy persons based on the totality of data in this submission, and a careful consideration of the biomedical literature. In the meantime, CBER will exercise regulatory flexibility in making products available to persons at high risk of severe disease of COVID-19, and at older age.

Specific Discussion:

Reference is made to Pfizer's two sBLAs [STN 125742/656 and STN 125742/696 (subsequently STN 125742/656.21)] received on 18 March, 2025 and 22 May 2025, respectively, and subsequent amendments received on or before August 25, 2025, through which Pfizer BioNTech (Applicant) sought supplemental approval of COVID-19 Vaccine, COMIRNATY, for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 5 years of age and older. CBER has concluded, for the reasons outlined below, that the BLA be limited to the following individuals at high risk of severe COVID-19 outcomes: those age 65 and older and those from 12 to 64 years with at least one high risk feature listed by the Centers for Disease Control and Prevention (CDC).[1] The Applicant submitted an amendment to the BLA revising their product labeling to align with this indication on May 12, 2025 and May 15, 2025. The Applicant's proposed changes are acceptable.

There are multiple reasons as to why CBER OD has decided to approve the BLA for individuals who are at high risk of severe outcomes from COVID-19 rather than a broad indication of all individuals 5 years and older. First, there are important limitations to the data submitted, including overreliance on potentially confounded observational data and a diminishing risk of severe outcomes from COVID-19 in the American population, coupled with known safety concerns, which fundamentally alter the benefit-risk calculation in non-high-risk individuals.

The randomized clinical trials of COVID-19 vaccines performed in 2020 and 2021 demonstrated acceptable efficacy against symptomatic COVID-19. Subsequent efficacy assessments for updated vaccine formulations against omicron subvariants have been based on immunogenicity data and observational or real-world data. Our ability to estimate clinical efficacy against novel COVID-19 variants from these types of studies is limited because the amount of protection conferred by an increase in neutralizing antibodies is unclear.[2] A 2025 observational study found antibody response to be significantly correlated with protection against self-reported repeat infection.[3] Although individuals with the highest neutralizing antibodies titers were found to have fewer repeat infections, it is unclear if the protection stemmed from factors innate to these individuals rather than from the absolute quantity of antibodies. Protection against future severe COVID-19 may predominantly come from other facets of the immune system, such as innate immunity or cell mediated immunity.[4,3] A causal relationship between a rise in neutralizing antibody titers and a diminished risk of severe COVID-19 outcomes has not been established, nor has the precise strength of such a relationship.

To date, FDA's regulatory approach for updated formulations of the SARS-CoV-2 vaccines has been similar to FDA's historical approach to updated yearly influenza vaccines. SARS-CoV-2 and influenza virus differ in important ways. First, infection with SARS-CoV-2 has been shown to provide durable protection against future severe disease and death, which appears to outlast protection conferred by vaccination.[5] Second, the rate of viral evolution of SARS-CoV-2 is markedly slower than influenza virus. One analysis estimated SARS-CoV-2 has a replication rate 24-fold lower than influenza virus.[6] This slower rate of evolution is reflected in the 2025 World Health Organization's analysis and recommendation that updates in the JN.1 and KP.2 antigen targets are unlikely to be necessary for the upcoming 2025-2026 formula of COVID-19 vaccines.[7] The slower rate of viral evolution of SARS-CoV-2 is also consistent with the more robust protection against severe COVID-19 observed in subsequent seasons following prior infection[5] which may be mediated by cellular immunity[4] and is seen to a much lesser extent with the influenza virus.[8]

Observational data, which has generally been supportive of risk reduction from additional vaccine doses, is subject to multiple categories of bias, including, but not limited to healthy vaccinee bias, which limits our ability to draw conclusions about vaccine efficacy. This bias is rooted in the fact that individuals seeking additional doses have different demographic characteristics, risk seeking, and health affirming behavior than those who do not, precluding reliable causal inference. This bias has been thoroughly documented for the COVID-19 and the influenza vaccine in numerous countries across the world.[9,10,11,12,13] Crucially, this bias was clearly demonstrated shown in one of the pivotal observational studies used to approve the initial Pfizer BioNTech COVID-19 booster shots, rendering its conclusions that boosters protected against COVID-19 mortality highly uncertain.[14,15]

Second, the risk of severe outcomes from COVID-19 has decreased dramatically over the last four years.[16,17] The infection fatality rate is estimated to have decreased approximately 10-fold with the emergence of the Omicron subvariants coupled with increased prior immunity rates.[17] Therefore, individuals who were previously at low risk of severe outcomes from COVID-19 now have even lower and, in fact, minimal risk of death due to COVID-19. Already in 2022, the infection fatality rate among

adults <73 years old without medical comorbidities was estimated to be under 0.007%.[16] Cumulative 2024-2025 COVID-19 hospitalization rates in the United States were lower than the 2024-2025 influenza season.[18]

The decrease in the chance of developing severe COVID-19, means that the potential for absolute benefit from vaccination has simultaneously decreased. Even rare vaccination-related harms, both known and unknown, now have a higher chance of outweighing potential benefits in non-high-risk populations. Some harm-benefit analyses of mRNA COVID-19 vaccines suggested net harm of ongoing vaccination of low-risk populations.[19,20] Post vaccination myocarditis is a well-established risk of the Pfizer BioNTech vaccine,[21,22] which can have serious and lasting consequences[22,23] and the FDA has determined this continues to pose a risk with updated vaccine formulations[24] and multiple additional thrombotic risks have been identified.[25]

Although the FDA monitors the safety of all vaccines through post-market surveillance, it is important to acknowledge times at which the potential for benefit from vaccination among non-high-risk individuals is small and poorly defined.

While not a factor in my decision making, it is worth noting that a narrowed indication for the COVID-19 vaccine brings the United States into closer alignment with international consensus where yearly COVID-19 vaccinations are only recommended to groups who are felt to be at high risk of severe outcomes of COVID-19.[26] This was highlighted at the April 2025 ACIP meeting[26] and discussed in the FDA's framework for COVID-19 vaccine approvals, "An Evidence-Based Approach to Covid-19 Vaccination" published in the *New England Journal of Medicine* on May 20th, 2025.[27]

Because the absolute potential for benefit among non-high-risk groups is minimal and there is substantial uncertainty about current vaccine efficacy, FDA is approving an indication in a patient population for whom the clinical benefits of ongoing vaccination have a greater potential of outweighing the known risks. We have also requested and reached concurrence on a PMC study (Study 2), in which a prospective, randomized, saline placebo-controlled clinical study will be conducted to determine if there are additional patient populations for whom a favorable benefit-risk profile exists. A successful outcome from the agreed-upon study may be submitted to the BLA to support future labeling changes. The Applicant and CBER OCD agree that there is equipoise for such a study in individuals 50 through 65 years of age without risk factors, as illustrated by varying practice patterns among peer nations. The applicant's proposed PMC study and milestones are acceptable. The rationale for the sponsor to conduct and provide an immunogenicity post marketing study is to demonstrate that the antibody titers generated in the population to which the vaccine is now being applied in the absence of randomization are at least as robust as those generated in the randomized population.

Concurrent administration:

CBER OCD has a new evidence based philosophy for allowing the sponsor to make claims about concurrent administration of vaccines. In the past such claims (e.g. giving COVID-19 and influenza together) have been made on the basis of small randomized studies showing non-inferior antibody titers. Often non-inferiority is defined permissively with lower bound confidence intervals above 0.67 being considered satisfactory. Yet, the reality is that CBER is both unsure if such titers correspond to clinical protection, and whether the basis of this margin retains clinical efficacy. Moreover, such small trials are inherently incapable of adequately documenting safety signals. The studies are simply too small to identify potential increases in adverse events, which Americans may wish to know. Post marketing

studies are often incapable of shedding additional light because of their non-randomized nature, and the fact that people who chose to space out vaccines are different from those who get them together in ways beyond the receipt of the vaccine.

At this time, CBER notes the following shift. First, CBER OCD acknowledges that concurrent administration offers the theoretical benefit of increasing compliance with annual respiratory pathogen vaccination. At the same time, the potential downside is that multiple vaccines administered together may interfere with efficacy—one or more vaccines may not be as effective—or there may be new or higher rates of safety signals that would not have occurred with sequential vaccination.

To adjudicate this question, CBER OCD will require pragmatic, randomized controlled trials, randomizing persons eligible for multiple vaccines to concomitantly administer them in a single session, or to administer some sequence of the vaccines. The trial could be performed with a hierarchical statistical design, testing first noninferiority and then superiority. The primary endpoint would be clinical, for instance: symptomatic RSV, COVID-19, and influenza. Secondary endpoints would be severe disease, and adverse events.

Such a trial could be initially designed for noninferiority of clinical events, but, because of increased compliance, and attrition in the sequential group, the trial could have a hierarchical superiority analysis. It is possible, but not certain, that concurrent administration will lead to superior outcomes. Finally, because this trial would be powered for clinical endpoints, there would be sufficient sample size to adjudicate important safety questions. Does the concurrent administration increase the rate of Bell's palsy by, for instance, 5, 10 or 20%? Such a trial may be able to ascertain even unexpected increases in safety signals. In the absence of such studies, FDA cannot affirm that concurrent administration is both safe and effective.

Conclusion:

I acknowledge that the USPI includes safety and immunogenicity data in individuals 5 years of age and older, with and without high-risk conditions. Although the indication has been revised to exclude some of these individuals, I concur with inclusion of this additional information within the USPI. I believe availability of this additional information will facilitate transparency and ensure that all available safety and immunogenicity data is available to the US public.

Finally, and although this is not a factor in my decision making, I note that there is emerging consensus in the American medical community with regards to the approach and reasoning presented in this memorandum. On February 25, 2025 former FDA commissioner, Robert Califf, indicated in the Journal of the American Medical Association: "Covid vaccine uptake is now low enough that large RCTs are feasible to evaluate the efficacy and safety of new updated boosters."[28] He confirmed this view on May 9th, 2025, on his personal Substack[29] writing: "In the case of COVID-19 I believe it would now be quite reasonable, and even advisable, to conduct placebo-controlled trials for 'boosters' using updated versions of the vaccine in people who are not high-risk."

In light of the considerations detailed here, I have concluded that this application should be approved under section 351(a) of the Public Health Service Act.

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