Exhibit 8

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLORADO

DANIEL ROBERT and **HOLLI MULVIHILL** Plaintiffs, v. **LLOYD AUSTIN**, in his official capacity as Secretary of Defense; **XAVIER BECERRA**, in his official capacity as Secretary of Health and Human Services; and **JANET WOODCOCK**, in her official capacity as Acting Commissioner of the U.S. Food and Drug Administration, Defendants.	Case No. 1:21-cv-02228-RM-STV

DECLARATION OF PETER MARKS, M.D., Ph.D.

I, Peter Marks, declare as follows:

1. I am the Director of the Center for Biologics Evaluation and Research ("CBER"), United States Food and Drug Administration ("FDA"), a position I have held since 2016. In this role, I direct the development and implementation of programs and policies for assuring the safety, purity, and potency of biological products, including vaccines, allergenic products, blood and blood products, and cellular, tissue, and gene therapies.

2. I joined FDA in 2012 as the Deputy Director for CBER, after practicing medicine, and working in industry and academia for several years. I received my graduate degree in cell and molecular biology and my medical degree at New York University, am board certified in internal medicine, hematology and medical oncology, and am a Fellow of the American College of Physicians.

3. In my capacity as Director of CBER, I am fully familiar with the instant matter and the facts stated herein. This declaration is based on my personal knowledge, my background, training, and experience and my review and consideration of information available to me in my official capacity, including information furnished by FDA personnel in the course of their official duties. My conclusions have been reached in accordance therewith.

4. Vaccines are biological products that are regulated under the Public Health Service Act ("PHSA"), 42 U.S.C. § 262(i)(1), as well as "drugs" subject to regulation under the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 321(g)(1)(B). Vaccines are approved for marketing through applications known as Biologics License Applications ("BLA"); a vaccine that is the subject of an approved BLA need not also obtain approval of a new drug application ("NDA") under 21 U.S.C. § 355. 42 U.S.C. § 262(a), (j).

5. Under the PHSA, FDA approves a BLA on the basis of a demonstration that: (1) the vaccine is "safe, pure, and potent"[1]; (2) the facility in which the vaccine is produced meets standards designed to assure that the vaccine continues to be safe, pure, and potent; and (3) the applicant consents to inspection of the manufacturing facility. 42 U.S.C. § 262(a)(2)(C). FDA may, but is not required to, consult with its standing advisory committee with scientific expertise in biological products, the Vaccines and Related Biological Products Advisory Committee, as part of the approval process. *See* 21 C.F.R. § 14.171(a). FDA has also issued several guidances and other public documents on biologics and vaccine development. *See generally* Biologics License Applications (BLA) Process, https://www.fda.gov/vaccines-blood-

[1] The standard for licensure of a biological product as potent under 42 U.S.C. § 262 has long been interpreted by FDA to include effectiveness. *See* 21 C.F.R. § 600.3(s); FDA Guidance, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products at 4 (May 1998), available at https://www.fda.gov/media/71655/download.

biologics/development-approval-process-cber/biologics-license-applications-bla-process-cber; Guidance, Compliance & Regulatory Information (Biologics), https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics; Vaccine and Related Biological Product Guidances, https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/vaccine-and-related-biological-product-guidances; Vaccine Development 101, https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-development-101.

6. On August 23, 2021, FDA approved a BLA for a COVID-19 vaccine known as Comirnaty, for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. *See* Comirnaty Approval Letter (August 23, 2021), attached as Exhibit A. Comirnaty is a mRNA vaccine. It contains a piece of the SARS-CoV-2 virus's genetic material that instructs cells in the body to make the virus's distinctive "spike" protein. After a person is vaccinated, their body produces copies of the spike protein, which does not cause disease, and triggers the immune system to learn to react defensively, producing an immune response against SARS-CoV-2. After delivering instructions, the mRNA is rapidly broken down. It does not enter the nucleus of the cell and does not affect DNA.

7. Prior to approval, beginning in December 2020, the same formulation of the vaccine, known as Pfizer-BioNTech Covid-19 vaccine, was available under an emergency use authorization ("EUA"). *See* https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19. FDA has discretion to issue an EUA for an FDA-regulated product if: (1) the Secretary of the Department of Health and Human Services has declared a public health emergency involving a biological or

other agent that can cause a serious or life-threatening disease or condition; (2) it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing that disease or condition, and the known and potential benefits of the product outweigh the known and potential risks of the product; and (3) there is no "adequate, approved, and available" alternative to the product. 21 U.S.C. § 360bbb-3(c).[2]

8. Even after FDA approved Comirnaty, FDA authorized continued use of the Pfizer-BioNTech Covid-19 vaccine under an EUA for indications that included the approved use. FDA determined that there is not sufficient approved vaccine available for distribution to the 16 years and older population in its entirety at the time of FDA's reissuance of the EUA. *See* Letter to Pfizer, Inc. reissuing EUA authorization for Covid-19 vaccine, p. 8, n.15 (November 19, 2021), attached as Exhibit B. FDA also determined that there are no products that are approved to prevent COVID-19 in additional populations covered by the EUA, as the vaccine remains available under the EUA for uses that have not been approved, specifically for individuals ages 5 through 15 years old; for a third dose in certain populations; and for a "booster" dose in certain circumstances.

9. The licensed vaccine has the same formulation as the originally authorized Pfizer-BioNTech vaccine. The products are legally distinct with certain differences that do not impact safety or effectiveness. Exhibit B at 10.

10. On October 29, 2021, FDA authorized a new formulation of the Pfizer-BioNTech vaccine for use in children 5 to 11 years of age when diluted to a lower strength. *Id.* at 2-3 n.12.

[2] Distribution of a product pursuant to an EUA is not a "clinical trial" subject to the requirements for clinical trials conducted under an investigational new drug ("IND") application. 21 U.S.C. §§ 360bbb-3(k); 355(i). Clinical trials must be conducted in accordance with an approved IND and involve only enrolled study participants. Only clinical trial participants enrolled in a clinical study conducted according to an approved IND receive the study drug.

FDA also authorized the new formulation, without dilution, for individuals 12 years of age and older. *Id.* The new formulation contains the same mRNA and lipids, and the same quantity of these ingredients, per 0.3 mL dose. *Id.* at 10. The two formulations differ only with respect to certain inactive ingredients and have been shown to be analytically comparable. *Id.* Therefore, FDA determined that "for individuals 12 years of age and older, COMIRNATY (COVID-19 Vaccine, mRNA) and the[] two formulations of the Pfizer-BioNTech COVID-19 Vaccine, when prepared according to their respective instructions for use, can be used interchangeably without presenting any safety or effectiveness concerns." *Id.* at 11. FDA provided this information in the Letter of Authorization to make clear that pharmacies and other healthcare practitioners could provide the vaccination series to recipients using Pfizer-BioNTech, Comirnaty, or both (*e.g.*, first dose of Pfizer-BioNTech followed by second dose of Comirnaty, or vice versa), since the products have an identical formulation and are made by the same manufacturer under current good manufacturing practice requirements. FDA included this clarification in the authorization letter to avoid the unnecessary operational complications that may have resulted if pharmacies or other healthcare practitioners had believed that the authorization did not include use in individuals who had received Pfizer-BioNTech for the first dose and Comirnaty for the second dose, or vice versa. Nevertheless, for individuals 12 years of age and older, only the original formulation is available at this time in the United States. *See* https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine. As a result, all currently available Pfizer-BioNTech vaccine in the United States for use in individuals 12 years of age and older has the same formulation as the approved Comirnaty vaccine.

11. The determination that FDA made for Comirnaty and Pfizer-BioNTech Covid-19

vaccine should not be confused with the statutory interchangeability determination that FDA may make when reviewing a BLA for a biological product manufactured by one company and comparing it with a biological product manufactured by a different company. Under 42 U.S.C. § 262(k)(4), FDA may determine that a biological product is "interchangeable" with a "reference product." "Reference product" is defined at 42 U.S.C. § 262(i)(4) as a "single biological product licensed under [42 U.S.C. § 262(a)] against which a biological product is evaluated in an application submitted under [42 U.S.C. § 262(k)]." The statutory interchangeability determination requires a licensed reference product and a subsequent applicant seeking licensure, which is not present here. The PHSA interchangeability provision also contains obligations related to exclusivity and exchange of patent information for interchangeable products, which would not make sense for two products produced by a single company. *See* 42 U.S.C. § 242(k)(6), (*l*).

12. While FDA determined Comirnaty and Pfizer-BioNTech Covid-19 vaccine are medically interchangeable, there are legal distinctions between BLA-approved and EUA-authorized products. For example, products approved under BLAs are required to have the labeling that was approved as part of the BLA, whereas products authorized under the EUA would have the EUA labeling, and there may also be differences in manufacturing sites for BLA and EUA vaccine. Both the EUA and BLA processes have required the sponsor to identify specific facilities that will manufacture the vaccine. *See* Summary Basis for Regulatory Action – Comirnaty, pp. 12-13 (August 23, 2021), available at https://www.fda.gov/media/151733/download.

13. Vaccine manufactured at sites listed in the BLA also undergoes lot release, which is designed to ensure conformity with standards applicable to the product. 21 C.F.R. § 610.1; *see*

also https://www.fda.gov/vaccines-blood-biologics/biologics-post-market-activities/lot-release#lotrelease. Vaccine manufactured at sites that are not listed in the BLA is not subject to the lot release requirement.[3] Manufacturing of the BLA and EUA vaccine must adhere to FDA's current good manufacturing practice regulations, which are designed to ensure that the products meet specified standards of safety, purity, and potency. *See* 21 C.F.R. Part 211 (CGMP regulations for drugs), § 211.1(b) (applicability of CGMP regulations to drugs that are also biological products); Exhibit B at 15.

14. In conjunction with the approval of Comirnaty, FDA asked the applicant to identify available lots of vaccine that were manufactured at facilities listed in the BLA that had undergone lot release. For these lots and other lots produced at facilities listed in the BLA, at this time, FDA is exercising its enforcement discretion with respect to certain labeling requirements, in that FDA is not taking enforcement with respect to vials that bear the EUA label.[4] FDA considers these lots to be manufactured in compliance with the BLA and they are not subject to the EUA requirements when used for the approved indication. Thus, the conditions in the Letter of Authorization for the EUA—including the condition requiring vaccination providers to provide recipients with the Fact Sheet for Recipients, which advises recipients that "under the EUA, it is your choice to receive or not receive the vaccine"—do not apply when these lots or

[3] Although not subject to lot release, as a condition of the EUA, Pfizer submits to the EUA file Certificates of Analysis for each drug product lot at least 48 hours prior to vaccine distribution; these Certificates include the established specifications and specific results for each quality control test performed on the final drug product lot. Additionally, also as a condition of the EUA, Pfizer submits quarterly manufacturing reports to the EUA file that include specified information about each lot of vaccine manufactured. *See* Exhibit B at 15.

[4] Each vial contains six doses of vaccine and a dose is withdrawn from the vial immediately before injection into a recipient, who would not ordinarily be handling the vial or viewing its label. Fact Sheet for Healthcare Providers Administering Vaccine, pp. 6-12 (Oct. 29, 2021), available at https://www.fda.gov/media/153713/download.

other BLA-compliant lots are used for the approved indication. FDA worked with the Applicant to develop a Dear Health Care Provider letter and website to identify those lots. Summary Basis for Regulatory Action – Comirnaty ("SBRA"), p. 27 (Nov. 8, 2021), attached as Exhibit C. Also, for operational efficiency, to account for the fact that recipients may receive either the BLA or EUA vaccine, after licensure of Comirnaty, vaccine has been distributed with unified Fact Sheets, one for providers and one for recipients, that provide information regarding the EUA product, as well as information about the licensed product. *See* Fact Sheet for Recipients and Caregivers 12 Years of Age and Older (Oct. 29, 2021), available at https://www.fda.gov/media/153716/download.

15. FDA has programs to expedite the development of drugs that are being studied to treat life-threatening or severely debilitating diseases. 21 U.S.C. § 356. These programs, one of which is "Fast Track" designation, are designed to help ensure that therapies for serious conditions are approved and available for patients as soon as it can be concluded that the therapies' benefits outweigh their risks. *See* Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014), available at https://www.fda.gov/media/86377/download. Fast Track designation was granted for Comirnaty on July 7, 2020. *See* Exhibit C, SBRA at 5. As explained on FDA's website, "Once a drug receives *Fast Track* designation, early and frequent communication between the FDA and a drug company is encouraged throughout the entire drug development and review process. The frequency of communication assures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients." https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track.

16. In addition to granting Comirnaty "Fast Track" designation, FDA took other steps to speed development and review of COVID-19 vaccines in response to the urgent public health threat posed by SARS-CoV-2, without sacrificing the stringent statutory requirements for approval. Vaccines typically undergo three phases of clinical trial. *See* https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-development-101. Phase 1 generally involves 20 to 100 healthy volunteers and focuses on safety. *Id.* Phases 2 and 3 studies typically enroll more subjects and are designed to gather more safety information on common short-term side effects and risks, examine the relationship between the dose administered and the immune response, and generate critical efficacy data. *Id.* In the case of the COVID-19 vaccines, those phases overlapped to speed the development process; no phases were skipped. *See* 21 C.F.R. § 312.21 ("Although in general the phases are conducted sequentially, they may overlap."). Also, because COVID-19 continues to be widespread, the vaccine clinical trials have been conducted more quickly than if the disease were less common.

17. The Comirnaty BLA was approved based on six months of safety and efficacy data from two ongoing clinical trials, C4591001 and BNT162-01, as well as safety information from the millions of vaccine doses administered under the EUA. C4591001 is a randomized, placebo-controlled, combined Phase 1, 2, and 3 study that has enrolled more than 43,000 participants. *See* Exhibit C, SBRA at 15. Initially, during Phases 2 and 3, study participants, as well as study investigators/personnel collecting and evaluating safety and efficacy information were blinded to the participants' treatment assignment (observer-blinded).[5] The study population for Phase 2/3

[5] "Blind" means that one or more parties of the clinical trial are kept unaware of the treatment assignment. Study participants, investigators, and health care providers may all be blinded to the treatment a participant is receiving, for example, whether a study participant is receiving the

includes participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19, such as participants working in the healthcare field, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. *Id.* at 16.

18. In accordance with C4591001's study protocol (the plan that describes the objectives, design, methodology, statistical considerations, and organization of a clinical trial, *see* Glossary of Clinical Trial Terms, *available at* https://www.fda.gov/media/108378/download#:~:text=A%20document%20that%20describes%20the,in%20other%20protocol%20referenced%20documents), participants ages 16 and older in C4591001 have been progressively "unblinded" since the December 2020 issuance of the EUA for the Pfizer-BioNTech Covid-19 vaccine and offered the vaccine if they were randomized to the placebo group. Exhibit C, SBRA at 17. The study was unblinded in stages, either when participants were eligible according to local recommendations for vaccination or after conclusion of their six-month post–Dose 2 study visit (whichever was earlier). *Id.* Despite the unblinding, the data collected during the clinical trial still allowed FDA to evaluate the safety and effectiveness of the vaccine, considering the data collected during the blinded stage and the other information submitted supporting safety and effectiveness. Although C4591001 is ongoing and

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study drug or a placebo. Glossary of Clinical Trial Terms, *available at* https://www.fda.gov/media/108378/download#:~:text=A%20document%20that%20describes%20the,in%20other%20protocol%20referenced%20documents). Blinding may be done to prevent skewing of the data by the placebo effect, by risk-seeking behavior, by unconscious bias or by other factors. Blinding may impose a significant burden on the volunteer trial participants, and medical ethicists generally agree that researchers are sometimes ethically bound to unblind a study and permit placebo recipients to receive an effective treatment at some point. The knowledge that treatment will be made available at some point to placebo recipients if it proves to be effective also encourages participation in clinical trials. Overall, the decision regarding when to "unblind" a clinical trial involves a delicate balance of competing priorities.

safety will be evaluated for the duration of the study for blinded and unblinded participants, because most adverse events linked to vaccination occur within two months of vaccination (*see* Table VI. National Vaccine Injury Compensation Program. Rockville, MD: Health Resources and Services Administration, 2017, https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf), FDA determined that a BLA for a COVID-19 vaccine could be supported by six months of safety data.[6] *See* FDA Guidance, Development and Licensure of Vaccines to Prevent COVID-19, at 15 (June 2020), attached as Exhibit D. Because the applicant submitted sufficient safety and efficacy data, the ongoing nature of the phase 3 clinical trial was not a basis for declining to license Comirnaty. The estimated completion date for C4591001 is May 2023, *see* https://www.clinicaltrials.gov/ct2/show/NCT04368728?term=C4591001&draw=2&rank=4).

19. BNT162-01 an ongoing Phase 1/2, open-label, dose-finding study with 24 participants, designed to evaluate the safety and immunogenicity of several candidate vaccines, including the dose that was approved by FDA on August 23, 2021. *See* Exhibit C, SBRA at 15. Safety data from the study was included in the BLA for Comirnaty and supported selection of the final vaccine candidate and dose level. *Id*. at 21. Although FDA did not refer the BLA to its

[6] Indeed, requesting six-months of follow-up safety data is not unique to Covid-19 vaccines. *See* Guidance for Industry Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines, at 5,7, 10 (May 2007), available at https://www.fda.gov/files/vaccines, blood & biologics/published/Guidance-for-Industry--Clinical-Data-Needed-to-Support-the-Licensure-of-Pandemic-Influenza-Vaccines.pdf (generally recommending six-months of safety data to support influenza vaccines). FDA explained the rationale for requesting at least six-months of safety data to support licensure of Comirnaty in its response to a Citizen Petition submitted by the Informed Consent Action Network ("ICAN"), raising concerns similar to those raised by Plaintiffs. *See* Response to ICAN Citizen Petition, Docket FDA-2021-P-0529, at 9-10 (August 23, 2021), available at https://www.regulations.gov/document/FDA-2021-P-0529-1077.

advisory committee, the agency considered the committee's feedback from prior meetings considering the EUA for the Pfizer-BioNTech Covid-19 vaccine. *Id.* at 26-27.

20. In addition to reviewing clinical data, before approving the Comirnaty BLA, FDA assessed, among other things, its chemistry, manufacturing, and controls ("CMC"); nonclinical and clinical pharmacology and nonclinical toxicology data; safety and pharmacovigilance data; labeling; and manufacturing facilities. *See* 21 C.F.R. § 601.2 (requirements for contents of BLA application). Along with the Summary Basis for Regulatory Action for Comirnaty, also available on FDA's website for the Comirnaty BLA review are three Statistical Reviews; an assessment of Real World Evidence; two Pharmacovigilance Plan Reviews; two CMC Reviews, Clinical Review; CBER Sentinel Program Sufficiency Review; Bioresearch Monitoring Review; Benefit-Risk Assessment Review; Analytical Method Review; and Toxicology Review. *See* https://www.fda.gov/vaccines-blood-biologics/comirnaty (click on Approval History, Letters, Reviews, and Related Document – COMIRNATY).

21. FDA approved Comirnaty based on data from the two clinical studies that demonstrated that the overall efficacy rate in the 16 and older subject population was 91.1% for the prevention of COVID-19 infection and between 95% and 100% for the avoidance of severe infection. Exhibit C, SBRA at 19-20. FDA also considered the safety data from the two clinical studies, in addition to safety information from EUA use. *Id.* at 22-25. In sum, based on its review of the clinical, pre-clinical, and product-related data submitted in the Comirnaty BLA, FDA determined that the product had a favorable benefit/risk balance, and was safe, pure, and potent. The agency approved the license for Comirnaty on August 23, 2021. *Id.* at 27-28; Exhibit A, FDA Approval Letter (Aug. 23, 2021).

22. Comirnaty is subject to specified post market requirements and commitments. *See* 21 U.S.C. §§ 355(o)(2)(B)(ii) and 356b. Those requirements and commitments are: (1) Study C4591009, entitled "A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY; (2) Study C4591021, entitled "Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY; (3) Study C4591021 sub-study to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY; (4) Study C4591036, a prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination; (5) Study C4591007 sub-study to prospectively assess the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age; (6) Study C4591031 sub-study to prospectively assess the incidence of subclinical myocarditis following administration of a third dose of COMIRNATY in a subset of participants 16 to 30 years of age; (7) Study C4591022, entitled "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)/MotherToBaby Pregnancy Registry"; (8) Study C4591007 sub-study to evaluate the immunogenicity and safety of lower dose levels of COMIRNATY in individuals 12 through < 30 years of age; (9) Study C4591012, entitled "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"; (10) Study C4591014, entitled

"Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California"; (11) Deferred pediatric study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age; (12) Deferred pediatric study C4591007 to evaluate the safety and effectiveness of COMIRNATY in children 6 months to < 12 years of age; and (13) Deferred pediatric study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants < 6 months of age. Exhibit C, SBRA at 29-30.

23. FDA also collects adverse event reports from the general population receiving the vaccine via the Vaccine Adverse Event Reporting System (VAERS). VAERS is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed or authorized in the United States. VAERS reports provide a very important tool in monitoring vaccine safety, but these reports alone cannot be used to determine if a vaccine caused or contributed to an adverse event or illness. *See* VAERS Data Disclaimer, https://vaers.hhs.gov/data.html. There are particular scientific limitations in comparing VAERS reports for COVID-19 vaccines with reports for previously approved vaccines for other conditions. For example, under the EUAs for the authorized COVID-19 vaccines, unlike for previously approved vaccines, vaccination providers are required to report to VAERS serious adverse events following vaccination with the COVID-19 vaccines "irrespective of attribution to vaccination" and regardless of how long after vaccination the adverse event occurs. In addition, CDC deployed the smartphone-based active-surveillance "v-safe" system only for the COVID-19 vaccines. V-safe has solicited adverse event reports directly from patients, which are then included in VAERS, but this system has only been deployed for COVID-19 vaccines and not for other vaccines. Finally, another potential factor that limits comparisons between VAERS reports for COVID-19 vaccines and reports for

other vaccines is the concept of "stimulated reporting." Because of extensive media coverage and awareness of the public health emergency – and of the authorized COVID-19 vaccines and their reported side effects – vaccine recipients, health care providers, and others are more likely to report adverse events for these vaccines than for other vaccines that have been widely available for longer periods of time. Although VAERS is not designed to assess causality, FDA and CDC actively monitor VAERS reports and engage in additional studies or investigations if VAERS monitoring suggests that a vaccine might be causing a health problem. *See* Children's Health Defense Petition Response, Docket FDA-2021-P-0460, at 17-28 (Aug. 23, 2021), attached as Exhibit E.

24. On the same day that FDA approved the license for Comirnaty, the agency responded to a Citizen Petition submitted by the Coalition Advocating for Adequately Licensed Medicines (CAALM) on July 23, 2021. CAALM Petition, Docket FDA-2021-P-0786, attached as Exhibit F. Among other things, the petition requested that FDA require "substantial evidence of clinical effectiveness that outweighs harms in special populations such as: infants, children, and adolescents; those with past SARS-CoV-2 infection; immunocompromised; pregnant women; nursing women; frail older adults; and individuals with cancer, autoimmune disorders, and hematological conditions" before licensing a Covid-19 vaccine, and that there should be information about "what kind of efficacy" exists for these populations, referring to "reduction in risk of symptomatic COVID-19 vs. reduction in risk of hospitalization or death." *Id.* at 2. Some of the populations identified by petitioners participated in the clinical trials and additional information will be obtained from post-marketing studies. For example, approximately 3% of the clinical trial participants had evidence of prior COVID-19 infection (*see* Clinical Review Memo at 35, referenced in paragraph 20, above). Additionally, although pregnant individuals

were excluded from participation in the trial and the applicant has committed to study the vaccine in this population segment as described in paragraph 22 above, participants in both the treatment and placebo arms of the trial became pregnant during the trial, and pregnancy outcomes of spontaneous abortion, miscarriages and elective abortions was similar between the vaccine and the placebo group. *Id.* at 84. In response to CAALM's Citizen Petition, FDA concluded that petitioners had not provided sufficient scientific justification for requiring effectiveness data from clinical trials specific to each population group and specifically designed to evaluate disease endpoints of varying severity, and petitioner's argument was not consistent with "scientifically valid methods of assessing safety and effectiveness," such as immunobridging or extrapolation across population groups. CAALM Petition Response, Docket FDA-2021-P-0786, at 7-8, attached as Exhibit G.

25. FDA also considered and responded to petitioner's claims that people previously affected with COVID-19 "are likely to have immunity to subsequent infections for as long or longer than immunity conferred by vaccine" and "may also be at heightened risk for adverse effects" from the vaccine, finding there was scientific uncertainty about the duration of immunity from natural infection and that petitioners had not provided sufficient scientific support for the latter claim. CAALM Petition Response at 8-9, n.31. In reaching that conclusion, FDA evaluated each study put forward by petitioners and carefully explained why the studies did not support petitioner's arguments. *Id.; see also* Response to ICAN Citizen Petition at 13-15. To the contrary, while there is scientific uncertainty about the duration of protection provided by previous natural infection, evidence is emerging that people get better protection by being fully vaccinated compared with having had COVID-19 natural infection. *See* CDC, COVID-19 Frequently Asked Questions, last updated August 2021, https://www.cdc.gov/coronavirus/2019-

ncov/vaccines/faq.html; Boyton, R. and D Altmann, 2021, Risk of SARS-CoV-2 reinfection after natural infection, Lancet, 397(10280):1161-1163, https://doi.org/10.1016/S0140-6736(21)00662-0. In addition, FDA and CDC medical officers conduct on-going active surveillance of serious adverse event reports for COVID-19 vaccines, including examination of narrative and other fields of adverse event reports that allow participants to input relevant information, which could include information about past COVID-19 infection. The reviewers conducting these surveillance efforts have not identified patterns of adverse events associated with receiving a COVID-19 vaccine after prior COVID-19 infection. *See* CAALM Petition Response at 8-9, n.31. In summary, FDA has not observed a heightened risk of adverse events for people who receive a COVID-19 vaccine after natural infection, either in the Comirnaty clinical study population (which included participants with evidence of prior COVID-19 infection) or in adverse event reports from the general population.

26. Safety surveillance reports received by FDA and CDC identified the risk of myocarditis and pericarditis following administration of Comirnaty. Comirnaty Summary Basis for Regulatory Action at 23 (Nov. 8, 2021). Reporting rates for medical chart-confirmed myocarditis/pericarditis in VAERS have been higher among males under 40 years of age than among females and older males and have been highest in males 12-17 years of age (65 cases per million doses administered as per CDC communication on August 20, 2021), particularly following the second dose, and onset of symptoms within 7 days following vaccination. *Id.* Although some cases of vaccine-associated myocarditis/pericarditis required intensive care support, available data from short-term follow up suggest that the large majority of individuals have had resolution of symptoms with conservative management. *Id.* Because vaccine-associated myocarditis/pericarditis is the most clinically significant identified risk, FDA

developed a quantitative model to compare the excess risk of myocarditis/pericarditis to the expected benefits of preventing COVID-19 and associated hospitalizations, ICU admissions, and deaths. *Id.* at 24. The model used an estimate of risk of myocarditis/pericarditis far higher than the rates estimated from reports to VAERS and assessed the benefit over a range of COVID-19 prevalence scenarios. *Id.* For males and females 18 years of age and older, even before accounting for morbidity prevented from non-hospitalized COVID-19, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under all conditions examined. *Id.*[7] FDA further adopted measures to mitigate the risk of myocarditis/pericarditis, including through labeling statements, continued safety surveillance, postmarketing studies (as described in Paragraph 22), and prescriber information and public health messaging. *Id.* Myocarditis remains a manageable adverse event with risks that are far outweighed by the benefits of preventing COVID-19, including the resultant risks of death, hospitalization, and myocarditis induced by COVID-19.

27. In approving the BLA for Comirnaty, FDA applied its scientific expertise to evaluate the data contained in the application and determined that Comirnaty's benefits outweigh its risks and that it is safe, pure, potent, and effective for its proposed use. In response to the urgent public health emergency presented by COVID-19, FDA worked expeditiously to provide

[7] The same was true for females 16-17 years of age. *Id.* For males 16-17 years of age, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under the "most likely" scenario, but that predicted excess cases of vaccine-associated myocarditis/pericarditis would exceed COVID-19 hospitalizations and deaths under the "worst case" scenario. *Id.* However, this predicted numerical imbalance does not account for the greater severity and length of hospitalization, on average, for COVID-19 compared with vaccine-associated myocarditis/pericarditis. *Id.* It also does not account for the risks of non-hospitalized COVID-19, or the societal benefits of vaccination. *Id.*

guidance to entities seeking to develop vaccines for this disease, and to review the BLA for Comirnaty once it was submitted to the agency to ensure it fully met the statutory standards for approval, to further the objective of protecting the public health.

28. An injunction affecting the licensure of Comirnaty would cause irreparable harm. Safe and effective vaccines are currently the most powerful tool we have against the pandemic and have been estimated to have already saved hundreds of thousands of lives. An injunction based on the Court's evaluation of the vaccine would call into question the data supporting FDA's determination that Comirnaty is safe and effective. The consequence could be to undermine the vaccine development process, if vaccine developers see that courts are willing to disregard FDA's rigorous review process and remove products from the market on the basis of mere allegations. In addition, another serious consequence could be to undermine the government's efforts to encourage vaccination in all eligible populations by exacerbating vaccine hesitancy. One of the most significant barriers to widespread vaccination is vaccine hesitancy and vaccine misinformation. It would also create considerable public and administrative confusion as to the effect of the injunction because the identical formulation has been authorized pursuant to an EUA. Even a more limited injunction, somehow limited to these plaintiffs, would generate extraordinary doubt and confusion.

I declare under penalty of perjury that the foregoing is true and correct to the best of my information, knowledge, and belief.

Dated: November 22, 2021

Peter Marks, M.D., Ph.D.
Director, Center for Biologics Evaluation
and Research
United States Food and Drug Administration

Marks Decl. Exhibit A

U.S. FOOD & DRUG ADMINISTRATION

Our STN: BL 125742/0 **BLA APPROVAL**

BioNTech Manufacturing GmbH August 23, 2021
Attention: Amit Patel
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Dear Mr. Patel:

Please refer to your Biologics License Application (BLA) submitted and received on May 18, 2021, under section 351(a) of the Public Health Service Act (PHS Act) for COVID-19 Vaccine, mRNA.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2229 to BioNTech Manufacturing GmbH, Mainz, Germany, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product, COVID-19 Vaccine, mRNA, which is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT04368728 and NCT04380701.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture COVID-19 Vaccine, mRNA drug substance at Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachusetts. The final formulated product will be manufactured, filled, labeled and packaged at Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs, Belgium and at Pharmacia & Upjohn Company LLC, 7000 Portage Road, Kalamazoo, Michigan. The diluent, 0.9% Sodium Chloride Injection, USP, will be manufactured at Hospira, Inc., (b) (4) and at Fresenius Kabi USA, LLC, (b) (4) .

You may label your product with the proprietary name, COMIRNATY, and market it in 2.0 mL glass vials, in packages of 25 and 195 vials.
We did not refer your application to the Vaccines and Related Biological Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for COVID-19 Vaccine, mRNA shall be 9 months from the date of manufacture when stored between -90ºC to -60ºC (-130ºF to -76ºF). The date of manufacture shall be no later than the date of final sterile filtration of the formulated drug product (at Pharmacia & Upjohn Company LLC in Kalamazoo, Michigan, the date of manufacture is defined as the date of sterile filtration for the final drug product; at Pfizer Manufacturing Belgium NV in Puurs, Belgium, it is defined as the date of the (b) (4) Following the final sterile filtration, (b) (4) , no reprocessing/reworking is allowed without prior approval from the Agency. The dating period for your drug substance shall be (b) (4) when stored at (b) (4) We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center

10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of COVID-19 Vaccine, mRNA, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including Package Insert, submitted under amendment 74, dated August 21, 2021, and the draft carton and container labels submitted under amendment 63, dated August 19, 2021.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the Package Insert submitted on August 21, 2021. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELS

Please electronically submit final printed carton and container labels identical to the carton and container labels submitted on August 19, 2021, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-certain-human-pharmaceutical-product-applications.

All final labeling should be submitted as Product Correspondence to this BLA STN BL 125742 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports at monthly intervals as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports-vaccines. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for ages younger than 16 years for this application because this product is ready for approval for use in individuals 16 years of age and older, and the pediatric studies for younger ages have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.28 and section 505B(a)(4)(C) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an "**Annual Status Report of Postmarketing Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. These required studies are listed below:

1. Deferred pediatric Study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age.

   Final Protocol Submission: October 7, 2020

   Study Completion: May 31, 2023

   Final Report Submission: October 31, 2023

2. Deferred pediatric Study C4591007 to evaluate the safety and effectiveness of COMIRNATY in infants and children 6 months to <12 years of age.

   Final Protocol Submission: February 8, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

3. Deferred pediatric Study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age.

   Final Protocol Submission: January 31, 2022

   Study Completion: July 31, 2024

   Final Report Submission: October 31, 2024

Submit the protocols to your IND 19736, with a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMR sequential number for each study/clinical trial and the submission number as shown in this letter.
Submit final study reports to this BLA STN BL 125742. In order for your PREA PMRs to be considered fulfilled, you must submit and receive approval of an efficacy or a labeling

supplement. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated as:

- **Required Pediatric Assessment(s)**

We note that you have fulfilled the pediatric study requirement for ages 16 through 17 years for this application.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of myocarditis and pericarditis and identify an unexpected serious risk of subclinical myocarditis.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following studies:

4. Study C4591009, entitled “A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States,” to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: August 31, 2021

   Monitoring Report Submission: October 31, 2022

   Interim Report Submission: October 31, 2023

   Study Completion: June 30, 2025

   Final Report Submission: October 31, 2025

5. Study C4591021, entitled “Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus

Disease 2019 (COVID-19) Vaccine," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY.

We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: August 11, 2021

Progress Report Submission: September 30, 2021

Interim Report 1 Submission: March 31, 2022

Interim Report 2 Submission: September 30, 2022

Interim Report 3 Submission: March 31, 2023

Interim Report 4 Submission: September 30, 2023

Interim Report 5 Submission: March 31, 2024

Study Completion: March 31, 2024

Final Report Submission: September 30, 2024

6. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: January 31, 2022

   Study Completion: March 31, 2024

   Final Report Submission: September 30, 2024

7. Study C4591036, a prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network).

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: November 30, 2021

   Study Completion: December 31, 2026

Final Report Submission: May 31, 2027

8. Study C4591007 substudy to prospectively assess the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this assessment according to the following schedule:

   Final Protocol Submission: September 30, 2021

   Study Completion: November 30, 2023

   Final Report Submission: May 31, 2024

9. Study C4591031 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a third dose of COMIRNATY in a subset of participants 16 to 30 years of age.

   We acknowledge the timetable you submitted on August 21, 2021, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: November 30, 2021

   Study Completion: June 30, 2022

   Final Report Submission: December 31, 2022

Please submit the protocols to your IND 19736, with a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMR sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to the BLA. If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement to this BLA STN BL 125742. For administrative purposes, all submissions related to these postmarketing studies required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise

undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letter of August 21, 2021 as outlined below:

10. Study C4591022, entitled “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)/MotherToBaby Pregnancy Registry.”

    Final Protocol Submission: July 1, 2021

Study Completion: June 30, 2025

Final Report Submission: December 31, 2025

11. Study C4591007 substudy to evaluate the immunogenicity and safety of lower dose levels of COMIRNATY in individuals 12 through <30 years of age.

    Final Protocol Submission: September 30, 2021

    Study Completion: November 30, 2023

    Final Report Submission: May 31, 2024

12. Study C4591012, entitled "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."

    Final Protocol Submission: January 29, 2021

    Study Completion: June 30, 2023

    Final Report Submission: December 31, 2023

13. Study C4591014, entitled "Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California."

    Final Protocol Submission: March 22, 2021

    Study Completion: December 31, 2022

    Final Report Submission: June 30, 2023

Please submit clinical protocols to your IND 19736, and a cross-reference letter to this BLA STN BL 125742 explaining that these protocols were submitted to the IND. Please refer to the PMC sequential number for each study/clinical trial and the submission number as shown in this letter.

If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence Study Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance
and Biologics Quality
Center for Biologics
Evaluation and Research

Marion F. Gruber, PhD
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

Marks Decl. Exhibit B

November 19, 2021

Pfizer Inc.
Attention: Mr. Amit Patel
235 East 42nd St
New York, NY 10017

Dear Mr. Patel:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or the Act), the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes Coronavirus Disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On December 11, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 for individuals 16 years of age and older pursuant to Section 564 of the Act. FDA reissued the letter of authorization on: December 23, 2020,[3] February 25, 2021,[4] May

[1] U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the FD&C Act, 21 U.S.C. § 360bbb-3, February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

[3] In the December 23, 2020 revision, FDA removed reference to the number of doses per vial after dilution from the letter of authorization, clarified the instructions for vaccination providers reporting to VAERS, and made other technical corrections. FDA also revised the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) to clarify the number of doses of vaccine per vial after dilution and the instructions for reporting to VAERS. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and the Fact Sheet for Recipients and Caregivers were revised to include additional information on safety monitoring and to clarify information about the availability of other COVID-19 vaccines.

[4] In the February 25, 2021 revision, FDA allowed flexibility on the date of submission of monthly periodic safety reports and revised the requirements for reporting of vaccine administration errors by Pfizer Inc. The Fact Sheet for Health Care Providers Administering Vaccine (Vaccination Providers) was revised to provide an update to the storage and transportation temperature for frozen vials, direct the provider to the correct CDC website for information on monitoring vaccine recipients for the occurrence of immediate adverse reactions, to include data from a developmental toxicity study, and add adverse reactions that have been identified during post authorization use. The Fact Sheet for Recipients and Caregivers was revised to add adverse reactions that have been identified during post authorization use.

10, 2021,[5] June 25, 2021,[6] and August 12, 2021.[7] On August 23, 2021, FDA approved COMIRNATY (COVID-19 Vaccine, mRNA)[8] and reissued the letter in its entirety for both Pfizer-BioNTech COVID-19 Vaccine and certain uses of COMIRNATY (COVID-19 Vaccine, mRNA).[9] Subsequently, FDA reissued the letter of authorization on September 22, 2021,[10] October 20, 2021,[11] and October 29, 2021.[12]

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[5] In the May 10, 2021 revision, FDA authorized Pfizer-BioNTech Vaccine for the prevention of COVID-19 in individuals 12 through 15 years of age, as well as for individuals 16 years of age and older. In addition, FDA revised the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) to include the following Warning: "Syncope (fainting) may occur in association with administration of injectable vaccines, in particular in adolescents. Procedures should be in place to avoid injury from fainting." In addition, the Fact Sheet for Recipients and Caregivers was revised to instruct vaccine recipients or their caregivers to tell the vaccination provider about fainting in association with a previous injection.

[6] In the June 25, 2021 revision, FDA clarified terms and conditions that relate to export of Pfizer-BioNTech COVID-19 Vaccine from the United States. In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was revised to include a Warning about myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine. The Fact Sheet for Recipients and Caregivers was updated to include information about myocarditis and pericarditis following administration of the Pfizer-BioNTech COVID-19 Vaccine.

[7] In the August 12, 2021 revision, FDA authorized a third dose of the Pfizer-BioNTech COVID-19 Vaccine administered at least 28 days following the two dose regimen of this vaccine in individuals 12 years of age or older who have undergone solid organ transplantation, or individuals 12 years of age or older who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

[8] COMIRNATY (COVID-19 Vaccine, mRNA) was approved for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.

[9] In the August 23, 2021 revision, FDA clarified that, subsequent to the FDA approval of COMIRNATY (COVID-19 Vaccine, mRNA) for the prevention of COVID-19 for individuals 16 years of age and older, this EUA would remain in place for the Pfizer-BioNTech COVID-19 Vaccine for the previously-authorized indication and uses. It also authorized COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA for certain uses that are not included in the approved biologics license application (BLA). In addition, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was revised to provide updates on expiration dating of the authorized Pfizer-BioNTech COVID-19 Vaccine and updated language regarding warnings and precautions related to myocarditis and pericarditis. The Fact Sheet for Recipients and Caregivers was updated as the Vaccine Information Fact Sheet for Recipients and Caregivers, which comprises the Fact Sheet for the authorized Pfizer-BioNTech COVID-19 Vaccine and information about the FDA-licensed vaccine, COMIRNATY (COVID-19 Vaccine, mRNA).

[10] In the September 22, 2021 revision, FDA authorized the administration of a single booster dose of COMIRNATY (COVID-19 Vaccine, mRNA) or Pfizer-BioNTech COVID-19 Vaccine at least 6 months after completing the primary series of this vaccine in individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

[11] In the October 20, 2021 revision, FDA clarified eligibility for the booster dose of COMIRNATY (COVID-19 Vaccine, mRNA) or Pfizer-BioNTech COVID-19 Vaccine and authorized the administration of a single booster dose of Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY (COVID-19 Vaccine, mRNA) as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine. The eligible population(s) and dosing interval for the heterologous booster dose are the same as those authorized for a booster dose of the vaccine used for primary vaccination.

[12] In the October 29, 2021 revision, FDA authorized: 1) the use of Pfizer-BioNTech COVID-19 Vaccine for children 5 through 11 years of age; and 2) a manufacturing change to include an additional formulation of the Pfizer-

On November 19, 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is again reissuing the October 29, 2021 letter of authorization in its entirety with revisions incorporated to amend the EUA for COMIRNATY (COVID-19 Vaccine, mRNA) and Pfizer-BioNTech COVID-19 Vaccine to authorize use of the vaccine as a single booster dose in individuals 18 years of age or older, at least 6 months after completing the primary series of this vaccine (i.e., as a homologous booster dose), and to authorize use of the vaccine as a single booster dose following completion of primary vaccination with another authorized COVID-19 vaccine (i.e., as a heterologous booster dose) in individuals 18 years of age or older. The dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination. The authorized uses, as well as the two formulations that have three presentations, are described in the Scope of Authorization section of this letter (Section II).

For the December 11, 2020 authorization for individuals 16 years of age and older, FDA reviewed safety and effectiveness data from an ongoing Phase 1/2/3 trial in approximately 44,000 participants randomized 1:1 to receive Pfizer-BioNTech COVID-19 Vaccine or saline control. The trial enrolled participants 12 years of age and older. FDA's review at that time considered the safety and effectiveness data as they relate to the request for emergency use authorization in individuals 16 years of age and older. FDA's review of the available safety data from 37,586 of the participants 16 years of age and older, who were followed for a median of two months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of the available efficacy data from 36,523 participants 12 years of age and older without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirmed that the vaccine was 95% effective (95% credible interval 90.3, 97.6) in preventing COVID-19 occurring at least 7 days after the second dose (with 8 COVID-19 cases in the vaccine group compared to 162 COVID-19 cases in the placebo group). Based on these data, and review of manufacturing information regarding product quality and consistency, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 16 years of age and older. Finally, on December 10, 2020, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

For the May 10, 2021 authorization for individuals 12 through 15 years of age, FDA reviewed safety and effectiveness data from the above-referenced, ongoing Phase 1/2/3 trial that enrolled approximately 46,000 participants, including 2,260 participants 12 through 15 years of age.

BioNTech COVID-19 Vaccine that uses tromethamine (Tris) buffer instead of phosphate buffered saline (PBS) used in the originally authorized Pfizer-BioNTech COVID-19 Vaccine. The formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer was authorized in two presentations: 1) Multiple dose vials, with gray caps and labels with a gray border, formulated to provide, without need for dilution, doses (each 0.3 mL dose containing 30 µg nucleoside-modified messenger RNA (modRNA)) for individuals 12 years of age and older; and 2) Multiple dose vials, with orange caps and labels with an orange border, formulated to provide, after dilution, doses (each 0.2 mL dose containing 10 µg modRNA) for individuals 5 through 11 years of age. The formulation that uses Tris buffer is the only formulation that is authorized for use in individuals 5 through 11 years of age.

Trial participants were randomized 1:1 to receive Pfizer-BioNTech COVID-19 Vaccine or saline control. FDA's review of the available safety data from 2,260 participants 12 through 15 years of age, who were followed for a median of 2 months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. FDA's analysis of SARS-CoV-2 50% neutralizing antibody titers 1 month after the second dose of Pfizer-BioNTech COVID-19 Vaccine in a subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection confirm that the geometric mean antibody titer in participants 12 through 15 years of age was non-inferior to the geometric mean antibody titer in participants 16 through 25 years of age. FDA's analysis of available descriptive efficacy data from 1,983 participants 12 through 15 years of age without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirm that the vaccine was 100% effective (95% confidence interval 75.3, 100.0) in preventing COVID-19 occurring at least 7 days after the second dose (with no COVID-19 cases in the vaccine group compared to 16 COVID-19 cases in the placebo group). Based on these data, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in individuals 12 through 15 years of age. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 12 through 15 years of age.

For the August 12, 2021 authorization of a third primary series dose in individuals 12 years of age or older who have undergone solid organ transplantation, or individuals 12 years of age or older who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise, FDA reviewed safety and effectiveness data reported in two manuscripts on solid organ transplant recipients. The first study was a single arm study conducted in 101 individuals who had undergone various solid organ transplant procedures (heart, kidney, liver, lung, pancreas) a median of 97±8 months earlier. A third dose of the Pfizer-BioNTech COVID-19 Vaccine was administered to 99 of these individuals approximately 2 months after they had received a second dose. Levels of total SARS-CoV-2 binding antibodies meeting the pre-specified criteria for success occurred four weeks after the third dose in 26/59 (44.0%) of those who were initially considered to be seronegative and received a third dose of the Pfizer-BioNTech COVID-19 Vaccine; 67/99 (68%) of the entire group receiving a third vaccination were subsequently considered to have levels of antibodies indicative of a significant response. In those who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 events were reported. A supportive secondary study describes a double-blind, randomized-controlled study conducted in 120 individuals who had undergone various solid organ transplant procedures (heart, kidney, kidney-pancreas, liver, lung, pancreas) a median of 3.57 years earlier (range 1.99-6.75 years). A third dose of a similar messenger RNA vaccine (the Moderna COVID-19 vaccine) was administered to 60 individuals approximately 2 months after they had received a second dose (i.e., doses at 0, 1 and 3 months); saline placebo was given to 60 individuals for comparison. The primary outcome was anti-RBD antibody at 4 months greater than 100 U/mL. This titer was selected based on NHP challenge studies as well as a large clinical cohort study to indicate this antibody titer was protective. Secondary outcomes were based on a virus neutralization assay and polyfunctional T cell responses. Baseline characteristics were comparable between the two study arms as were pre-intervention anti-RBD titer and neutralizing antibodies. Levels of total SARS-CoV-2 binding

antibodies indicative of a significant response occurred four weeks after the third dose in 33/60 (55.0%) of the Moderna COVID-19 vaccinated group and 10/57 (17.5%) of the placebo individuals. In the 60 individuals who received a third vaccine dose, the adverse event profile was similar to that after the second dose and no grade 3 or grade 4 adverse events were reported. Despite the moderate enhancement in antibody titers, the totality of data (i.e., supportive paper by Hall et al. demonstrated efficacy of the product in the elderly and persons with co-morbidities) supports the conclusion that a third dose of the Pfizer-BioNTech COVID-19 Vaccine may be effective in this population, and that the known and potential benefits of a third dose of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine for immunocompromised individuals at least 12 years of age who have received two doses of the Pfizer-BioNTech COVID-19 Vaccine and who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

For the September 22, 2021 authorization of a single booster dose administered at least 6 months after completing the primary series in individuals: 65 years of age and older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19, FDA reviewed safety and effectiveness data from the above-referenced, ongoing Phase 1/2/3 trial in which 329 participants 18 through 75 years of age received a booster dose of the Pfizer-BioNTech COVID-19 Vaccine approximately 6 months (range 4.8 to 8.8 months) after completion of the primary series. FDA's review of the available safety data from 329 participants 18 through 75 years of age, who had been followed for a median of 2.6 months after receiving the booster dose, did not identify specific safety concerns that would preclude issuance of an EUA. The effectiveness of the booster dose of the Pfizer-BioNTech COVID-19 Vaccine is based on an assessment of 50% neutralizing antibody titers (NT50) against SARS-CoV-2 (USA_WA1/2020). FDA's analysis of SARS-CoV-2 NT50 one month after the booster dose compared to 1 month after the primary series in study participants 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the booster dose confirmed noninferiority for both geometric mean ratio and difference in seroresponse rates. Based on the totality of the scientific evidence available, including data from the above-referenced clinical trial, FDA concluded that a booster dose the Pfizer-BioNTech COVID-19 Vaccine may be effective, and that the known and potential benefits of a single booster dose at least 6 months after completing the primary series outweigh the known and potential risks for individuals 65 years of age and older; individuals 18 through 64 years of age at high risk of severe COVID-19; and individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

For the October 20, 2021 authorization of a single booster dose as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine, FDA reviewed data from an ongoing Phase1/2 clinical trial in participants 19-85 years of age. In this trial, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose

series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrollment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Adverse events were assessed through 28 days after the booster dose. An overall review of adverse reactions reported following the Pfizer-BioNTech COVID-19 Vaccine heterologous booster dose did not identify any new safety concerns, as compared with adverse reactions reported following Pfizer-BioNTech COVID-19 Vaccine primary series doses or homologous booster dose. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Pfizer-BioNTech COVID-19 Vaccine was demonstrated regardless of primary vaccination. Based on the on the totality of the scientific evidence available, including data from the above-referenced clinical trial, FDA concluded that a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine may be effective, and that the known and potential benefits of a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine following completion of primary vaccination with another authorized COVID-19 vaccine outweigh the known and potential risks.

For the October 29, 2021 authorization for the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer for individuals 5 through 11 years of age, FDA reviewed safety and effectiveness data from an ongoing Phase 1/2/3 trial that has enrolled 4,695 participants 5 through 11 years of age, of whom 3,109 participants received Pfizer-BioNTech COVID-19 Vaccine (containing 10 µg modRNA) formulated using PBS buffer and approximately 1,538 participants received saline control in Phase 2/3. FDA's review of the available safety data from 3,109 participants 5 through 11 years of age who received Pfizer-BioNTech COVID-19 Vaccine (containing 10 µg modRNA), including 1,444 who were followed for at least 2 months after receiving the second dose, did not identify specific safety concerns that would preclude issuance of an EUA. SARS-CoV-2 50% neutralizing antibody titers 1 month after the second dose were compared between a subset of participants 5 through 11 years of age who received Pfizer-BioNTech COVID-19 Vaccine (containing 10 µg modRNA) and a subset of participants 16 through 25 years of age who received Pfizer-BioNTech COVID-19 Vaccine (containing 30 µg modRNA) in the above-referenced ongoing Phase 1/2/3 trial that enrolled approximately 46,000 participants. Immunobridging analyses included a subset of participants from each study who had no serological or virological evidence of past SARS-CoV-2 infection. FDA's analyses confirm that immunobridging criteria were met for both geometric mean antibody titers and seroresponse rates. FDA's analysis of available descriptive efficacy data from 1,968 participants 5 through 11 years of age without evidence of SARS-CoV-2 infection prior to 7 days after dose 2 confirm that the vaccine was 90.7% effective (95% confidence interval 67.7, 98.3) in preventing COVID-19 occurring at least 7 days after the second dose (with 3 COVID-19 cases in the vaccine group compared to 16 COVID-19 cases in the placebo group). Based on these data, FDA concluded that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in individuals 5 through 11 years of age. Additionally, FDA determined it is reasonable to conclude, based on the totality of the scientific evidence available, that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks of the vaccine, for the prevention of COVID-19 in individuals 5 through 11 years of age. Finally, on

October 26, 2021, the Vaccines and Related Biological Products Advisory Committee voted in agreement with this conclusion.

For the October 29, 2021 authorization of the manufacturing change to include an additional formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer instead of PBS buffer used in the originally authorized Pfizer-BioNTech COVID-19 Vaccine, FDA reviewed data on analytical comparability, which uses laboratory testing to demonstrate that a change in product formulation is not expected to impact safety or effectiveness. In the case of Pfizer-BioNTech COVID-19 Vaccine, multiple different release parameters were evaluated, ranging from product appearance to size of the lipid-nanoparticle to the integrity of the modRNA in the product. Release and characterization tests include tests for purity, composition, and critical attributes of mRNA associated with the activity of the vaccine. In this case, analytical comparability to the current PBS formulation of the Pfizer-BioNTech COVID-19 Vaccine was demonstrated for the Tris formulation of the Pfizer-BioNTech COVID-19 Vaccine through a combination of release and characterization testing.

For the November 19, 2021 authorization expanding the eligible population for the homologous and heterologous booster doses to individuals 18 years of age and older, FDA reviewed data provided by the sponsor and other data available to FDA, including real world evidence. Data previously reviewed to support the September 22, 2021 authorization of a homologous booster dose, together with new real-world data indicating increasing COVID-19 cases in the United States, including among vaccinated individuals, and suggesting a decreased risk of myocarditis following mRNA COVID-19 vaccine booster doses compared with second primary series doses, support expansion of the population eligible for a Pfizer-BioNTech COVID-19 vaccine homologous booster dose to include all individuals 18 years of age and older who completed the primary series at least 6 months previously. Data previously reviewed to support the October 20, 2021 authorization of a heterologous booster dose, together with data and information to support authorization of the EUA amendment to expand the eligible population for a homologous booster dose of the Moderna COVID-19 Vaccine, support a revision to the Pfizer-BioNTech COVID-19 Vaccine EUA such that the eligible population for a heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine is all adults 18 years of age and older who completed primary vaccination with another authorized COVID-19 vaccine. Based on the totality of the scientific evidence available, FDA concludes that a homologous or heterologous booster dose of the Pfizer-BioNTech COVID-19 Vaccine may be effective, and that the known and potential benefits of the booster dose of the Pfizer-BioNTech Vaccine following completion of primary vaccination with Pfizer-BioNTech COVID-19 Vaccine or another authorized COVID-19 vaccine, outweigh the known and potential risks in individuals 18 years of age and older.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Pfizer-BioNTech COVID-19 Vaccine[13] for the prevention of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization. Additionally, as specified in

[13] Reference to the Pfizer-BioNTech COVID-19 Vaccine hereinafter refers to both the PBS and Tris formulations, unless specifically delineated otherwise.

subsection III.BB., I am authorizing use of COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA as described in the Scope of Authorization section of this letter (Section II).

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of Pfizer-BioNTech COVID-19 Vaccine[14] for the prevention of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

A. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

B. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19, and that, when used under the conditions described in this authorization, the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine when used to prevent COVID-19 outweigh its known and potential risks; and

C. There is no adequate, approved, and available alternative[15] Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19.[16]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Pfizer Inc. will supply Pfizer-BioNTech COVID-19 Vaccine either directly or through authorized distributor(s),[17] to emergency response stakeholders[18] as directed by the U.S.

[14] In this section (Section I), references to Pfizer-BioNTech COVID-19 Vaccine also apply to COMIRNATY (COVID-19 Vaccine, mRNA).

[15] Although COMIRNATY (COVID-19 Vaccine, mRNA) is approved to prevent COVID-19 in individuals 16 years of age and older, there is not sufficient approved vaccine available for distribution to this population in its entirety at the time of reissuance of this EUA. Additionally, there are no COVID-19 vaccines that are approved to provide: COVID-19 vaccination in individuals 5 through 15 years of age; a third primary series dose to certain immunocompromised populations described in this EUA; a homologous booster dose to the authorized population described in this EUA; or a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine.

[16] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

[17] "Authorized Distributor(s)" are identified by Pfizer Inc. or, if applicable, by a U.S. government entity, such as the Centers for Disease Control and Prevention (CDC) and/or other designee, as an entity or entities allowed to distribute authorized Pfizer-BioNTech COVID-19 Vaccine.

[18] For purposes of this letter, "emergency response stakeholder" refers to a public health agency and its delegates that have legal responsibility and authority for responding to an incident, based on political or geographical boundary lines (e.g., city, county, tribal, territorial, State, or Federal), or functional (e.g., law enforcement or public health range) or sphere of authority to administer, deliver, or distribute vaccine in an emergency situation. In some cases (e.g., depending on a state or local jurisdiction's COVID-19 vaccination response organization and plans),

government, including the Centers for Disease Control and Prevention (CDC) and/or other designee, for use consistent with the terms and conditions of this EUA; and

- Pfizer-BioNTech COVID-19 Vaccine may be administered by a vaccination provider[19] without an individual prescription for each vaccine recipient.

For use in individuals 12 years of age and older

- The Pfizer-BioNTech COVID-19 Vaccine formulations that use Tris and PBS buffers (each 0.3 mL dose containing 30 µg modRNA), as described in more detail under *Product Description* below, covered by this authorization will be administered by vaccination providers and used only to prevent COVID-19 in individuals 12 years of age and older with a two-dose primary regimen (3 weeks apart) and to provide:
  - a third primary series dose at least 28 days following the second dose to individuals 12 years of age or older who have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise;
  - a single booster dose at least 6 months after completion of a primary series of the vaccine to individuals 18 years of age or older; and
  - a single booster dose as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine, in individuals 18 years of age and older, where the dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

For use in individuals 5 through 11 years of age

- The Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer (each 0.2 mL dose containing 10 µg modRNA), as described in more detail under *Product Description* below, covered by this authorization will be administered by vaccination providers and

there might be overlapping roles and responsibilities among "emergency response stakeholders" and "vaccination providers" (e.g., if a local health department is administering COVID-19 vaccines; if a pharmacy is acting in an official capacity under the authority of the state health department to administer COVID-19 vaccines). In such cases, it is expected that the conditions of authorization that apply to emergency response stakeholders and vaccination providers will all be met.

[19] For purposes of this letter, "vaccination provider" refers to the facility, organization, or healthcare provider licensed or otherwise authorized by the emergency response stakeholder (e.g., non-physician healthcare professionals, such as nurses and pharmacists pursuant to state law under a standing order issued by the state health officer) to administer or provide vaccination services in accordance with the applicable emergency response stakeholder's official COVID-19 vaccination and emergency response plan(s) and who is enrolled in the CDC COVID-19 Vaccination Program. If the vaccine is exported from the United States, a "vaccination provider" is a provider that is authorized to administer this vaccine in accordance with the laws of the country in which it is administered. For purposes of this letter, "healthcare provider" also refers to a person authorized by the U.S. Department of Health and Human Services (e.g., under the PREP Act Declaration for Medical Countermeasures against COVID-19) to administer FDA-authorized COVID-19 vaccine (e.g., qualified pharmacy technicians and State-authorized pharmacy interns acting under the supervision of a qualified pharmacist). See, e.g., HHS. *Fourth Amendment to the Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19 and Republication of the Declaration*. 85 FR 79190 (December 9, 2020).

used only to prevent COVID-19 in individuals 5 through 11 years of age with a two-dose primary regimen (3 weeks apart).

For use in individuals who are 11 years old at the time of the first dose, and turn 12 years old before the second dose:

- Notwithstanding the age limitations for use of the different formulations and presentations described above, individuals who will turn from 11 years to 12 years of age between their first and second dose in the primary regimen may receive, for either dose, either: (1) the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer (each 0.2 mL dose containing 10 µg modRNA) covered by this authorization; or (2) the Pfizer-BioNTech COVID-19 Vaccine and COMIRNATY formulations provided in one of the presentations for individuals 12 years of age and older (each 0.3 mL dose containing 30 µg modRNA) covered by this authorization.
- The vaccine will be administered by vaccination providers and used only to prevent COVID-19 with a two-dose primary regimen (3 weeks apart).

This authorization also covers the use of the licensed COMIRNATY (COVID-19 Vaccine, mRNA) product when used to provide: (1) a two-dose primary regimen (0.3 mL each, 3 weeks apart) for individuals 12 through 15 years of age; (2) a third primary series dose at least 28 days following the second dose to individuals 12 years of age or older who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise; (3) a single booster dose (0.3 mL) at least 6 months after completion of the primary series to individuals 18 years of age and older; and (4) a single booster dose (0.3 mL) as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine in individuals 18 years of age and older, where the dosing interval for the heterologous booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.

The Pfizer-BioNTech COVID-19 Vaccine that uses PBS buffer and COMIRNATY (COVID-19 Vaccine, mRNA) have the same formulation. The products are legally distinct with certain differences that do not impact safety or effectiveness. Accordingly, under this EUA, the Pfizer-BioNTech COVID-19 Vaccine that uses PBS buffer and COMIRNATY (COVID-19 Vaccine, mRNA) can be used interchangeably as described above, without presenting any safety or effectiveness concerns.

As described below under *Product Description*, the Pfizer-BioNTech COVID-19 Vaccine formulations that use Tris and PBS buffers, which are covered by this authorization for use in individuals 12 years of age and older, contain the same modRNA and lipids, and the same quantity of these ingredients, per 0.3 mL dose. The two formulations differ with respect to certain inactive ingredients only and have been shown to be analytically comparable.[20]

[20] Analytical comparability assessments use laboratory testing to demonstrate that a change in product formulation does not impact a product's safety or effectiveness. For the Pfizer-BioNTech COVID-19 Vaccine, multiple different release parameters were evaluated to assess the comparability of the modified formulation (the formulation with the Tris buffer) to the originally-authorized formulation (the formulation with the PBS buffer). These release parameters ranged from product appearance to size of the lipid-nanoparticle to the integrity of the modRNA in the

Accordingly, under this EUA, for individuals 12 years of age and older, COMIRNATY (COVID-19 Vaccine, mRNA) and these two formulations of the Pfizer-BioNTech COVID-19 Vaccine, when prepared according to their respective instructions for use, can be used interchangeably without presenting any safety or effectiveness concerns.

Therefore, for individuals 12 years of age and older, COMIRNATY (COVID-19 Vaccine, mRNA) is authorized to complete the primary regimen or provide a booster dose for individuals who received their initial primary dose(s) with the Pfizer-BioNTech COVID-19 Vaccine (whether the PBS formulation or Tris formulation), and the Pfizer-BioNTech COVID-19 Vaccine (whether the PBS formulation or Tris formulation) is authorized to complete the primary regimen or provide a booster for individuals who received their initial primary dose(s) with COMIRNATY (COVID-19 Vaccine, mRNA).

Product Description[21]

The Pfizer-BioNTech COVID-19 Vaccine, supplied in two formulations, is provided in three different vials:

For use in individuals 12 years of age and older

- The Pfizer-BioNTech COVID-19 Vaccine that uses PBS buffer is available in multiple dose vials with purple caps. It is formulated to provide, after dilution, 0.3 mL doses (each containing 30 μg modRNA) and can be used for all authorized indications in individuals 12 years of age and older.
- The Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer, and is available in multiple dose vials with gray caps and labels with gray borders, is formulated to provide, after dilution, 0.3 mL doses (each containing 30 μg modRNA) and can be used for all authorized indications in individuals 12 years of age and older.

For use in individuals 5 through 11 years of age

- The Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer, and is available in multiple dose vials with orange caps and labels with orange borders, is formulated to provide, after dilution, 0.2 mL doses (each containing 10 μg modRNA) and can be used for administration to individuals 5 through 11 years of age.

For use in individuals 12 years of age and older

The Pfizer-BioNTech COVID-19 Vaccine that uses PBS buffer (supplied in multiple dose vials with purple caps) is supplied as a frozen suspension; each vial must be diluted with 1.8 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. The Pfizer-

product. Release and characterization tests include tests for purity, composition, and critical attributes of mRNA associated with the activity of the vaccine. The combination of release testing and characterization testing demonstrated that the modified formulation is analytically comparable to the original formulation.

[21] For COMIRNATY (COVID-19 Vaccine, mRNA) product description, please see the COMIRNATY (COVID-19 Vaccine, mRNA) prescribing information, found here: *https://www.fda.gov/media/151707/download.*

BioNTech COVID-19 Vaccine does not contain a preservative. Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 μg of modRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2. Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylee glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. The diluent (0.9% Sodium Chloride Injection) contributes an additional 2.16 mg sodium chloride per dose.

The Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer and that is supplied in multiple dose vials with gray caps is supplied as a frozen suspension and should not be diluted. The Pfizer-BioNTech COVID-19 Vaccine does not contain a preservative. Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 μg of a modRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2. Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.19 mg cholesterol), 0.06 mg tromethamine, 0.4 mg tromethamine hydrochloride, and 31 mg sucrose.

For use in individuals 5 through 11 years of age

The Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer and that is supplied in multiple dose vials with orange caps is supplied as a frozen suspension; each vial must be diluted with 1.3 mL of sterile 0.9% Sodium Chloride Injection, USP prior to use to form the vaccine. Each dose of the Pfizer-BioNTech COVID-19 Vaccine contains 10 μg of a modRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2. Each dose of the Pfizer-BioNTech COVID-19 Vaccine also includes the following ingredients: lipids (0.14 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.02 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.03 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.06 mg cholesterol), 10.3 mg sucrose, 0.02 mg tromethamine, and 0.13 mg tromethamine hydrochloride. The diluent (0.9% Sodium Chloride Injection, USP) contributes 0.9 mg sodium chloride per dose.

The manufacture of the authorized Pfizer-BioNTech COVID-19 Vaccine is limited to those facilities identified and agreed upon in Pfizer's request for authorization.

The Pfizer-BioNTech COVID-19 Vaccine vial label and carton labels are clearly marked for "Emergency Use Authorization." The Pfizer-BioNTech COVID-19 Vaccine is authorized to be distributed, stored, further redistributed, and administered by emergency response stakeholders when packaged in the authorized manufacturer packaging (i.e., vials and cartons), despite the fact that the vial and carton labels may not contain information that otherwise would be required under the FD&C Act.

Pfizer-BioNTech COVID-19 Vaccine is authorized for emergency use with the following product-specific information required to be made available to vaccination providers and recipients, respectively (referred to as "authorized labeling"):

- Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) - For 12 Years of Age and Older Dilute Before Use
- Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) - For 12 Years of Age and Older Do Not Dilute
- Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers): Emergency Use Authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19) - For 5 Through 11 Years of Age Dilute Prior To Use
- Vaccine Information Fact Sheet for Recipients and Caregivers About COMIRNATY (COVID-19 Vaccine, mRNA) and Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease (COVID-19) For Use in Individuals 12 Years of Age and Older
- Vaccine Information Fact Sheet for Recipients and Caregivers About the Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease (COVID-19) for Use in Individuals 5 Through 11 Years of Age

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine,[22] when used to prevent COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that Pfizer-BioNTech COVID-19 Vaccine may be effective in preventing COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that Pfizer-BioNTech COVID-19 Vaccine (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of Pfizer-BioNTech COVID-19 Vaccine under this EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), Pfizer-BioNTech COVID-19 Vaccine is authorized to prevent COVID-19 as described in

[22] The conclusions supporting authorization stated in this section (Section II) also apply to COMIRNATY (COVID-19 Vaccine, mRNA).

the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Pfizer Inc. and Authorized Distributor(s)

A. Pfizer Inc. and authorized distributor(s) will ensure that the authorized Pfizer-BioNTech COVID-19 Vaccine is distributed, as directed by the U.S. government, including CDC and/or other designee, and the authorized labeling (i.e., Fact Sheets) will be made available to vaccination providers, recipients, and caregivers consistent with the terms of this letter.

B. Pfizer Inc. and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until delivered to emergency response stakeholders' receipt sites.

C. Pfizer Inc. will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., emergency response stakeholders, authorized distributors, and vaccination providers) involved in distributing or receiving authorized Pfizer-BioNTech COVID-19 Vaccine. Pfizer Inc. will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized labeling.

D. Pfizer Inc. may develop and disseminate instructional and educational materials (e.g., video regarding vaccine handling, storage/cold-chain management, preparation, disposal) that are consistent with the authorized emergency use of the vaccine as described in the letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs during an emergency. Any instructional and educational materials that are inconsistent with the authorized labeling are prohibited.

E. Pfizer Inc. may request changes to this authorization, including to the authorized Fact Sheets for the vaccine. Any request for changes to this EUA must be submitted to Office of Vaccines Research and Review (OVRR)/Center for Biologics Evaluation and Research (CBER). Such changes require appropriate authorization prior to implementation.[23]

[23] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), or (7), review and concurrence is required from the Preparedness and Response Team (PREP)/Office of the Center Director (OD)/CBER and the Office of Counterterrorism and Emerging Threats (OCET)/Office of the Chief Scientist (OCS).

F. Pfizer Inc. will report to Vaccine Adverse Event Reporting System (VAERS):
- Serious adverse events (irrespective of attribution to vaccination);
- Cases of Multisystem Inflammatory Syndrome in children and adults; and
- Cases of COVID-19 that result in hospitalization or death, that are reported to Pfizer Inc.

These reports should be submitted to VAERS as soon as possible but no later than 15 calendar days from initial receipt of the information by Pfizer Inc.

G. Pfizer Inc. must submit to Investigational New Drug application (IND) number 19736 periodic safety reports at monthly intervals in accordance with a due date agreed upon with the Office of Biostatistics and Epidemiology (OBE)/CBER beginning after the first full calendar month after authorization. Each periodic safety report is required to contain descriptive information which includes:
- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest;
- A narrative summary and analysis of vaccine administration errors, whether or not associated with an adverse event, that were identified since the last reporting interval;
- Newly identified safety concerns in the interval; and
- Actions taken since the last report because of adverse experiences (for example, changes made to Healthcare Providers Administering Vaccine (Vaccination Providers) Fact Sheet, changes made to studies or studies initiated).

H. No changes will be implemented to the description of the product, manufacturing process, facilities, or equipment without notification to and concurrence by FDA.

I. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

J. Pfizer Inc. will submit to the EUA file Certificates of Analysis (CoA) for each drug product lot at least 48 hours prior to vaccine distribution. The CoA will include the established specifications and specific results for each quality control test performed on the final drug product lot.

K. Pfizer Inc. will submit to the EUA file quarterly manufacturing reports, starting in July 2021, that include a listing of all Drug Substance and Drug Product lots produced after issuance of this authorization. This report must include lot number, manufacturing site, date of manufacture, and lot disposition, including those lots that were quarantined for investigation or those lots that were rejected. Information on the reasons for lot quarantine or rejection must be included in the report.

L. Pfizer Inc. and authorized distributor(s) will maintain records regarding release of Pfizer-BioNTech COVID-19 Vaccine for distribution (i.e., lot numbers, quantity, release date).

M. Pfizer Inc. and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

N. Pfizer Inc. will conduct post-authorization observational studies to evaluate the association between Pfizer-BioNTech COVID-19 Vaccine and a pre-specified list of adverse events of special interest, including myocarditis and pericarditis, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Pfizer-BioNTech COVID-19 Vaccine under this EUA in the general U.S. population (5 years of age and older), individuals who receive a booster dose, populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The studies should be conducted in large scale databases with an active comparator. Pfizer Inc. will provide protocols and status update reports to the IND 19736 with agreed-upon study designs and milestone dates.

Emergency Response Stakeholders

O. Emergency response stakeholders will identify vaccination sites to receive authorized Pfizer-BioNTech COVID-19 Vaccine and ensure its distribution and administration, consistent with the terms of this letter and CDC's COVID-19 Vaccination Program.

P. Emergency response stakeholders will ensure that vaccination providers within their jurisdictions are aware of this letter of authorization, and the terms herein and any subsequent amendments that might be made to the letter of authorization, instruct them about the means through which they are to obtain and administer the vaccine under the EUA, and ensure that the authorized labeling [i.e., Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and Vaccine Information Fact Sheet for Recipients and Caregivers] is made available to vaccination providers through appropriate means (e.g., e-mail, website).

Q. Emergency response stakeholders receiving authorized Pfizer-BioNTech COVID-19 Vaccine will ensure that appropriate storage and cold chain is maintained.

Vaccination Providers

R. Vaccination providers will administer the vaccine in accordance with the authorization and will participate and comply with the terms and training required by CDC's COVID-19 Vaccination Program.

S. Vaccination providers will provide the Vaccine Information Fact Sheet for Recipients and Caregivers to each individual receiving vaccination and provide the necessary information for receiving their second dose and/or third dose.

T. Vaccination providers administering the vaccine must report the following information associated with the administration of the vaccine of which they become

aware to VAERS in accordance with the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers):

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in children and adults
- Cases of COVID-19 that result in hospitalization or death

Complete and submit reports to VAERS online at https://vaers.hhs.gov/reportevent.html. The VAERS reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report. More information is available at vaers.hhs.gov or by calling 1-800-822-7967. To the extent feasible, report to Pfizer Inc. by contacting 1-800-438-1985 or by providing a copy of the VAERS form to Pfizer Inc.; Fax: 1-866-635-8337.

U. Vaccination providers will conduct any follow-up requested by the U.S government, including CDC, FDA, or other designee, regarding adverse events to the extent feasible given the emergency circumstances.

V. Vaccination providers will monitor and comply with CDC and/or emergency response stakeholder vaccine management requirements (e.g., requirements concerning obtaining, tracking, and handling vaccine) and with requirements concerning reporting of vaccine administration data to CDC.

W. Vaccination providers will ensure that any records associated with this EUA are maintained until notified by FDA. Such records will be made available to CDC, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising, and Promotion

X. All descriptive printed matter, advertising, and promotional material, relating to the use of the Pfizer-BioNTech COVID-19 Vaccine shall be consistent with the authorized labeling, as well as the terms set forth in this EUA, and meet the requirements set forth in Section 502(a) and (n) of the FD&C Act and FDA implementing regulations.

Y. All descriptive printed matter, advertising, and promotional material relating to the use of the Pfizer-BioNTech COVID-19 Vaccine clearly and conspicuously shall state that:

- This product has not been approved or licensed by FDA, but has been authorized for emergency use by FDA, under an EUA to prevent Coronavirus Disease 2019 (COVID-19) for use either in individuals 12 years of age and older, or in individuals 5 through 11 years of age, as appropriate; and
- The emergency use of this product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of the medical product under Section 564(b)(1) of the FD&C Act unless the declaration is terminated or authorization revoked sooner.

Condition Related to Export

Z. If the Pfizer-BioNTech COVID-19 Vaccine is exported from the United States, conditions C, D, and O through Y do not apply, but export is permitted only if 1) the regulatory authorities of the country in which the vaccine will be used are fully informed that this vaccine is subject to an EUA and is not approved or licensed by FDA and 2) the intended use of the vaccine will comply in all respects with the laws of the country in which the product will be used. The requirement in this letter that the authorized labeling (i.e., Fact Sheets) be made available to vaccination providers, recipients, and caregivers in condition A will not apply if the authorized labeling (i.e., Fact Sheets) are made available to the regulatory authorities of the country in which the vaccine will be used.

Conditions With Respect to Use of Licensed Product

AA. COMIRNATY (COVID-19 Vaccine, mRNA) is licensed for individuals 16 years of age and older. There remains, however, a significant amount of Pfizer-BioNTech COVID-19 Vaccine that was manufactured and labeled in accordance with this emergency use authorization. The authorization remains in place with respect to the Pfizer-BioNTech COVID-19 Vaccine for this population.

BB. This authorization also covers the use of the licensed COMIRNATY (COVID-19 Vaccine, mRNA) product when used to provide: (1) a two-dose primary regimen for individuals 12 through 15 years of age;[24] (2) a third primary series dose to individuals 12 years of age or older who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise; (3) a single booster dose at least 6 months after completing the primary series to individuals 18 years of age or older; and (4) a heterologous booster dose in individuals 18 years of age and older who have completed primary vaccination with a different authorized COVID-19 vaccine as described in the Scope of Authorization (Section II) under this EUA. Conditions A through W in this letter apply when COMIRNATY (COVID-19 Vaccine, mRNA) is provided for the uses described in this subsection III.BB., except that product manufactured and labeled in accordance with the approved BLA is deemed to satisfy the manufacturing, labeling, and distribution requirements of this authorization.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

[24] As noted above, this includes the first dose of a two-dose primary regimen for individuals who are 11 years old and will turn 12 years of age between their first and second dose in the primary regimen.

Sincerely,

--/S/--

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Jacqueline A. O'Shaughnessy, Ph.D.
Acting Chief Scientist
Food and Drug Administration

Enclosures

Marks Decl. Exhibit C

Summary Basis for Regulatory Action

Date:	11/8/2021
From:	Ramachandra Naik, PhD, Review Committee Chair, DVRPA/OVRR
BLA STN:	125742/0
Applicant:	BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)
Submission Receipt Date:	May 18, 2021
PDUFA Action Due Date:	January 16, 2022
Proper Name:	COVID-19 Vaccine, mRNA
Proprietary Name:	COMIRNATY
Indication:	Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Vaccines Research and Review

_____

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OVRR) • Facilities Review (OCBQ/DMPQ) • Facilities Inspection (OCBQ/DMPQ and OVRR/DVP) • Lot Release, QC, Test Methods, Product Quality (OCBQ/DBSQC)	Xiao Wang, PhD, OVRR/DVP Anissa Cheung, MSc, OVRR/DVP Kathleen Jones, PhD, OCBQ/DMPQ Laura Fontan, PhD, OCBQ/DMPQ Gregory Price, PhD, OCBQ/DMPQ CDR Donald Ertel, MS, OCBQ/DMPQ Nicole Li, MS, OCBQ/DMPQ Christian Lynch, OCBQ/DMPQ Alifiya Ghadiali, OCBQ/DMPQ Zhongren Wu, PhD, OCBQ/DMPQ Ekaterina Allen, PhD, OCBQ/DMPQ Hsiaoling Wang, PhD, OCBQ/DBSQC Emnet Yitbarek, PhD, OCBQ/DBSQC Karla Garcia, MS, OCBQ/DBSQC Anil Choudhary, PhD, MBA, OCBQ/DBSQC Esmeralda Alvarado Facundo, PhD, OCBQ/DBSQC Marie Anderson, PhD, OCBQ/DBSQC Cheryl Hulme, OCBQ/DMPQ
Clinical • Clinical (OVRR) • Postmarketing Safety, Epidemiological Review (OBE/DE) • Real World Evidence • Benefit-Risk Assessment • BIMO	Susan Wollersheim, MD, OVRR/DVRPA CAPT Ann T. Schwartz, MD, OVRR/DVRPA Lucia Lee, MD, OVRR/DVRPA Deborah Thompson, MD, MSPH, OBE/DE Yun Lu, PhD, OBE Hong Yang, PhD, OBE Osman Yogurtcu, PhD, OBE Patrick Funk, PhD, OBE Haecin Chun, MT (ASCP) SSB, MS, OCBQ/DIS
Statistical • Clinical Data (OBE/DB) • Nonclinical Data	Lei Huang, PhD, OBE/DB Ye Yang, PhD, OBE/DB Xinyu Tang, PhD, OBE/DB
Nonclinical/Pharmacology/Toxicology • Toxicology (OVRR) • Developmental Toxicology (OVRR)	Nabil Al-Humadi, PhD, OVRR/DVRPA
Labeling • Promotional (OCBQ/APLB) • Carton and Container Labels • Labeling Review	CAPT Oluchi Elekwachi, PharmD, MPH, OCBQ/APLB Daphne Stewart, OVRR/DVRPA Laura Gottschalk, PhD, OVRR/DVRPA
• Consults (CDISC, Datasets) • Documentation Review	Brenda Baldwin, PhD, OVRR/DVRPA CAPT Michael Smith, PhD, OVRR/DVRPA
Advisory Committee Summary	No Advisory Committee meeting held

Table of Contents

1. Introduction

BioNTech Manufacturing GmbH (in partnership with Pfizer Inc.) submitted a Biologics License Application (BLA) STN BL 125742 for licensure of COVID-19 Vaccine, mRNA. The proprietary name of the vaccine is COMIRNATY. COMIRNATY is a vaccine indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The vaccine is administered intramuscularly (IM) as a series of two 30 µg doses (0.3 mL each) 3 weeks apart.

COMIRNATY (also referred to as BNT162b2 in this document) contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2 that is formulated in lipids including ((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.

COMIRNATY is supplied as a concentrated multi-dose liquid formulation (0.45 mL volume) stored frozen at -90°C to -60°C in a 2 mL Type 1 glass vial. A sterile diluent, 0.9% Sodium Chloride Injection, USP, is supplied separately in 2 mL glass vials manufactured by Fresenius Kabi LLC and in 10 mL vials manufactured by Hospira, Inc. The diluent is stored at 20°C to 25°C and will be shipped in parallel with shipments of COMIRNATY, with arrivals synchronized so that the diluent is delivered before the vaccine is delivered. Healthcare providers may also use other sources of sterile 0.9% Sodium Chloride Injection, USP as a diluent for COMIRNATY, if necessary.

The COMIRNATY Multiple Dose Vial is thawed in a refrigerator (2°C to 8°C) for 2 to 3 hours or at room temperature (up to 25°C) for 30 minutes. The vial must be warmed to room temperature for dilution. Once at room temperature, the COMIRNATY Multiple Dose Vial is diluted with 1.8 mL of the diluent. After dilution, each vial of COMIRNATY contain six doses of 0.3 mL of vaccine. Each 0.3 mL dose of COMIRNATY contains 30 µg of mRNA encoding the spike glycoprotein of SARS-CoV-2 and the following ingredients: lipids (0.43 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 2.52 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose. After dilution, the vials are stored at 2°C to 25°C and must be used within 6 hours from the time of dilution. COMIRNATY is preservative-free.

The expiry dating period for COMIRNATY Multiple Dose Vial is 9 months from the date of manufacture when stored at -90°C to -60°C. The date of manufacture shall be no later than the date of final sterile filtration of the formulated drug product (at Pharmacia & Upjohn Company LLC in Kalamazoo, Michigan, the date of manufacture is defined as the date of sterile filtration for the final drug product; at Pfizer-Manufacturing Belgium NV in Puurs, Belgium, it is defined as the date of the (b) (4) .

2. Background

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 and was identified in patients with pneumonia of unknown cause. The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus). SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV). SARS-CoV-2 is the causative agent of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of August 2021, has caused approximately 208 million cases of COVID-19, including 4.3 million deaths worldwide. In the United States (U.S.), more than 37 million cases have

been reported to the Centers for Disease Control and Prevention (CDC), of which 90% have occurred in individuals 16 years of age or older. While the pandemic has caused morbidity and mortality on an individual level, the continuing spread of SARS-CoV-2 and emerging variants has caused significant challenges and disruptions in worldwide healthcare systems, economies, and many aspects of human activity (travel, employment, education).

In the U.S., there are no licensed vaccines or anti-viral drugs for the prevention of COVID-19. In December 2020, the FDA issued emergency use authorizations (EUAs) for two mRNA vaccines which encode the SARS-CoV-2 spike glycoprotein: Pfizer-BioNTech COVID-19 Vaccine (manufactured by Pfizer, Inc. in partnership with BioNTech manufacturing GmbH) for use in individuals 16 years of age and older, and Moderna COVID-19 Vaccine (manufactured by ModernaTX, Inc.) for use in individuals 18 years of age and older. In February 2021, the FDA issued an EUA for a replication-incompetent adenovirus type 26 (Ad26)-vectored vaccine encoding a stabilized variant of the SARS-CoV-2 spike glycoprotein, manufactured by Janssen Biotech, Inc. (Janssen COVID-19 Vaccine) for use in individuals 18 years of age and older. In May 2021, the FDA expanded the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine to include adolescents 12 through 15 years of age. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under emergency use.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting (Written Responses)	April 6, 2020 (Part 1) April 10, 2020 (Part 2)
2. IND submission	April 22, 2020
3. Fast Track designation granted	July 7, 2020
4. Submission of EUA request for individuals ≥16 years of age	November 20, 2020
5. Issuance of EUA for individuals ≥16 years	December 11, 2020
6. Submission of EUA request for individuals 12-15 years of age	April 9, 2021
7. Issuance of EUA for individuals 12-15 years of age	May 10, 2021
8. Pre-BLA meeting (Written Responses)	Clinical: March 9, 2021 CMC: March 31, 2021
9. BLA STN 125742/0 received	May 18, 2021
10. BLA filed	July 15, 2021
11. Mid-Cycle communication	The Applicant canceled
12. Late-Cycle meeting	The Applicant canceled
13. Action Due Date	January 16, 2022

3. Chemistry, Manufacturing and Controls (CMC)

a. Product Quality

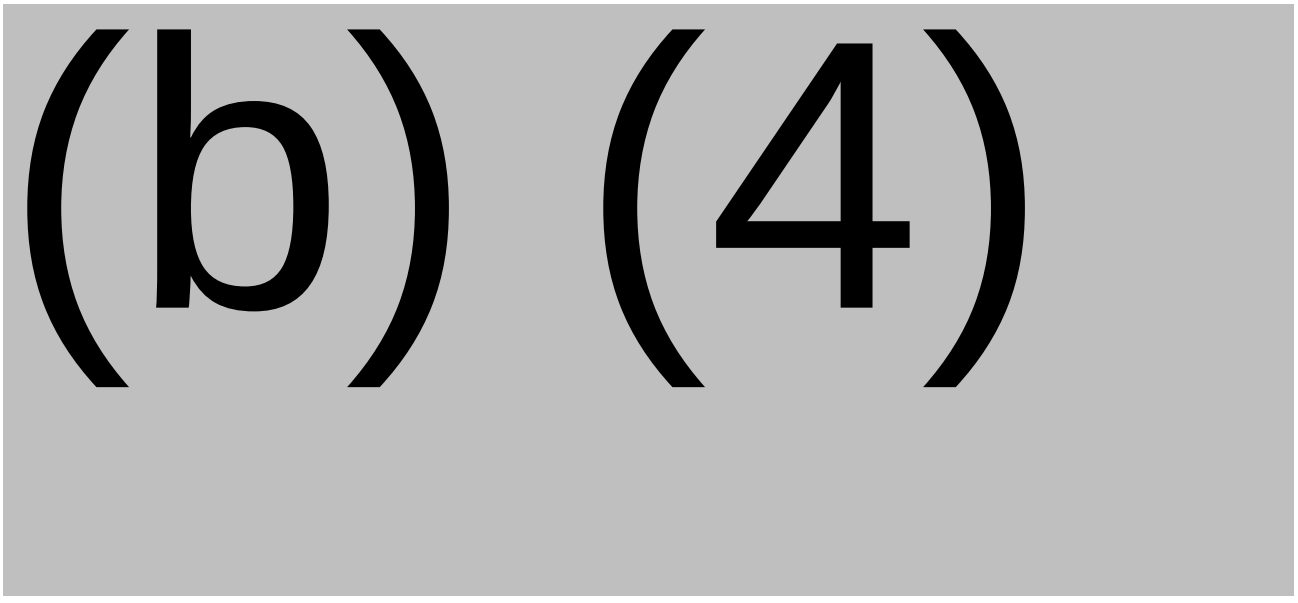
COMIRNATY Manufacturing Overview

COMIRNATY contains a nucleoside-modified messenger RNA (mRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2 that is formulated in lipids including ((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. COMIRNATY is supplied as a frozen suspension to be diluted with a diluent, 0.9% Sodium Chloride Injection, USP, that is supplied separately or can be acquired elsewhere, if necessary. Manufacture of the mRNA drug substance will take place in Andover, MA, USA. The final formulated drug product will be manufactured, filled, finished, labeled and packaged in Puurs, Belgium or in Kalamazoo, MI, USA. The 0.9% Sodium Chloride Injection, USP diluent will be manufactured by Fresenius-Kabi USA, LLC ((b) (4)) and Hospira, Inc. ((b) (4)).

The mRNA in COMIRNATY is a single-stranded, 5'-capped mRNA encoding the full-length SARS-CoV-2 spike glycoprotein derived from the Wuhan-Hu-1 isolate (GenBank MN908947.3 and GenBank QHD43416.1). The antigen-coding RNA sequence is codon-optimized and contains two proline mutations ((b) (4) 87P), which ensures an antigenically optimal trimerized pre-fusion confirmation (S-2P). The RNA also contains common structural elements, including 5'-cap, 5'-UTR, 3'-UTR, and poly(A) tail, all of which are designed for mediating high RNA stability and translation efficiency. During RNA transcription, (b) (4) is replaced with the (b) (4) . This nucleoside substitution has been demonstrated to enhance translation of *in vitro* transcribed mRNA while reducing its reactogenicity.

Drug Substance (DS)

The manufacture of mRNA DS is divided into (b) (4) major manufacturing process stages:



Drug Product (DP)

The manufacturing process of the DP is divided into the following critical steps:

- **Preparation of the DS:** (b) (4)
- **Formation of LNP:** In this step, (b) (4)
- **Formulation of the bulk DP:** The bulk DP is formulated by (b) (4)
- **Filling:** The bulk DP is sterile filtered and aseptically filled into 2 mL Type I borosilicate glass vials manufactured by (b) (4) .
- **Labeling and storage:** The filled vials are visually inspected, labeled, and frozen at -90°C to -60°C.

Composition

The composition of the formulation of COMIRNATY and the function of the ingredients are provided in Table 2.

Table 2. Composition of COMIRNATY Multiple Dose Vial

Ingredients	Amount per vial	Function
SARS-CoV-2 spike glycoprotein mRNA (UNII: 5085ZFP6SJ)	225 µg	Active Ingredient
ALC-0315 [4-hydroxybutyl)azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate) (UNII: AVX8DX713V)	3.23 mg	Lipid component
ALC-0159 [2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide] (UNII: PJH39UMU6H)	0.4 mg	Lipid component
DSPC [1,2-distearoyl-sn-glycero-3-phosphocholine] (UNII: 043IPI2M0K)	0.7 mg	Lipid component
Cholesterol (UNII: 97C5T2UQ7J)	1.4 mg	Lipid component
Potassium chloride (UNII: 660YQ98I10)	0.07 mg	Excipient
Monobasic potassium phosphate (UNII: 4J9FJ0HL51)	0.07 mg	Excipient
Sodium Chloride	2.7 mg	Excipient

Ingredients	Amount per vial	Function
(UNII: 451W47IQ8X)		
Dibasic sodium phosphate dihydrate (UNII: GR686LBA74)	0.49 mg	Excipient
Sucrose (UNII: C151H8M554)	46.0 mg	Excipient
Water for Injection (UNII: 059QF0KO0R)	q.s.	Excipient

UNII: Unique Ingredient Identifier
q.s. = quantum satis (as much as may suffice)

Stability of COMIRNATY in Multiple Dose Vial

For the long-term storage condition study, parameters monitored are Appearance, (b) (4) by (b) (4), LNP (b) (4), RNA content and (b) (4) Assay, Lipid (ALC-0315, ALC-0159, DSPC, and Cholesterol) Content by (b) (4), Container closure integrity test by (b) (4), Endotoxin content by (b) (4), and Sterility.

The stability data provided in the submission support a dating period of 9 months from the date of manufacture when stored at -90°C to -60°C for the COMIRNATY DP filled in 2 mL Type I borosilicate glass vials. Stability data on emergency use and process performance qualification lots also support storage at -20°C ± 5°C for up to 2 weeks as well as short term storage at 5°C ± 3°C for up to one month (within the 9-month expiry dating period).

The Diluent for COMIRNATY

The contents of the vaccine vial are diluted with sterile 0.9% Sodium Chloride Injection, USP. Vials of sterile 0.9% Sodium Chloride Injection, USP are provided but shipped separately. The provided diluent or another sterile 0.9% Sodium Chloride Injection, USP should be used as the diluent.

The provided 0.9% Sodium Chloride Injection, USP diluent will be supplied either as cartons of 10 mL single-use vials manufactured by Hospira, Inc (NDC 0409-4888-10), or 2 mL single-use vials manufactured by Fresenius Kabi USA, LLC (NDC 63323-186-02). The composition of the saline diluent and the function of the ingredients are provided in Table 3.

Table 3. Composition of the Diluent

Ingredients	Quantity (per 0.3 mL dose)	Function
SODIUM CHLORIDE (UNII: 451W47IQ8X)	2.16 mg	Excipient
Water for Injection (UNII: 059QF0KO0R)	0.3 mL	Excipient

UNII: Unique Ingredient Identifier

COMIRNATY

Product Composition

COMIRNATY Multiple Dose Vial is supplied as a frozen suspension that is diluted at the time of use with 1.8 mL of saline diluent. A single dose of COMIRNATY contains 30 ug mRNA in a volume of 0.3 mL, and it does not contain preservative. [*See section 10.b regarding exception to the 21 CFR 610.15(a) requirement for a preservative.*]

Stability of COMIRNATY

The Applicant conducted in-use stability studies to support the maximum temperature and time period that COMIRNATY can retain its physicochemical properties. Based on the data generated, COMIRNATY retains its quality attributes for up to 6 hours when stored between 2°C to 25°C (35°F to 77°F).

The carton labels and the Package Insert (PI) state that after dilution, vials should be stored between 2°C to 25°C (35°F to 77°F) and used within 6 hours from the time of dilution. During storage, exposure to room light should be minimized, and direct exposure to sunlight and ultraviolet light should be avoided. Any vaccine remaining in vials must be discarded after 6 hours and cannot be refrozen.

Assays used in clinical studies

Diagnostic Assays Used to Support Clinical Efficacy Endpoints

Two clinical diagnostic assays (Cepheid Xpert Xpress RT-PCR assay for the detection of SARS-CoV-2 in clinical specimens and Roche Elecsys Anti-SARS-CoV-2 assay for the evaluation of serostatus to SARS-CoV-2) were used to assess clinical endpoints. Both assays have received FDA authorization under EUA.

The Cepheid Xpert Xpress RT-PCR assay is a rapid, automated *in vitro* diagnostic test for the qualitative detection of the N and E gene sequences from nasopharyngeal, nasal, or mid-turbinate swab and/or nasal wash/aspirate specimens collected from patients suspected of having COVID-19. This assay is used to assess viral infection of the participants before vaccination and to confirm COVID-19 cases during study follow-up.

The Roche Elecsys Anti-SARS-CoV-2 assay is a rapid, automated *in vitro* diagnostic test for detecting the presence of antibodies to nucleocapsid (N) protein of SARS-CoV-2 (antigen not present in COMIRNATY) in serum or plasma samples. This is a qualitative assay marketed as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, which would indicate a recent or prior infection. This assay is used to assess serostatus of the participants before vaccination.

Data were submitted to support the suitability of both the Cepheid Xpert Xpress assay and the Roche Elecsys Anti-SARS-CoV-2 assay for their intended uses in Phase 2/3 clinical studies when performed at Pfizer's testing facility (Pfizer Vaccine Research and Development; Pearl River, NY).

Immunogenicity Assays Used for Exploratory Immunogenicity Endpoints

Two immunogenicity assays (SARS-CoV-2 mNeonGreen (mNG) virus microneutralization assay and (b) (4) direct Luminex assay (dLIA) for IgG

quantification) were used for evaluating the immune responses from clinical trial samples.

The SARS-CoV-2 mNG microneutralization assay measures neutralizing antibodies (50% inhibition titers) against SARS-CoV-2 using Vero cell monolayers in a 96-well plate format. The SARS-CoV-2 mNG virus is derived from the USA_WA1/2020 strain that had been rescued by reverse genetics and engineered to express a fluorescent reporter gene (mNeonGreen) upon productive infection of cells. The validation protocol (that includes evaluation of dilutional linearity, precision, limits of quantification, and limit of detection) and the results of the validation study, executed at Pfizer Hackensack Meridian Health Center (Nutley, New Jersey), were submitted to support the suitability of the assay for testing of clinical trial immunogenicity samples.

The (b) (4) S1 IgG dLIA measures IgG antibody levels to the subunit 1 (S1) of the SARS-CoV-2 spike protein in human serum samples. Qualification data provided in the submission support the (b) (4) dLIA for quantification of human IgG antibodies that bind to the S1 protein of SARS-CoV-2 and confirm that the assay is suitable for its intended use.

b. Testing Specifications

Specifications and Methods

The tests and specifications applied for routine release of COMIRNATY are shown in Table 4.

Table 4. Control of COMIRNATY: Tests and Specifications

Quality Attribute	Analytical Procedure	Acceptance Criteria
Appearance	Appearance (Visual)	White to off-white suspension
Appearance (Visible Particulates)	Appearance (Particles) (b) (4)	May contain white to off-white opaque, amorphous particles
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
LNP (b) (4)	(b) (4)	(b) (4)
LNP (b) (4)	(b) (4)	(b) (4)
RNA (b) (4)	(b) (4) assay	(b) (4)
RNA content	(b) (4) assay	(b) (4)
ALC-0315 content	(b) (4)	(b) (4)
ALC-0159 content	(b) (4)	(b) (4)
DSPC content	(b) (4)	(b) (4)
Cholesterol content	(b) (4)	(b) (4)
Vial content (volume)	Container content	Not less than (b) (4)
Lipid identities	(b) (4)	(b) (4) (ALC-0315, ALC-0159, Cholesterol, DSPC)

Quality Attribute	Analytical Procedure	Acceptance Criteria
Identity of encoded RNA	(b) (4)	Identity confirmed
(b) (4)	(b) (4)	(b) (4)
RNA (b) (4)	(b) (4)	(b) (4)
Bacterial Endotoxin	Endotoxin ((b) (4)) (b) (4)	(b) (4)
Sterility	Sterility ((b) (4))	No Growth Detected
Container Closure Integrity	(b) (4)	Pass

Abbreviations: LNP = Lipid nanoparticles; (b) (4)

The analytical methods and their validations and/or qualifications for the COMIRNATY DS and DP were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of COMIRNATY are listed in Table 5 below. The activities performed and inspectional histories are also noted in Table 5 and are further described in the paragraphs that follow.

Table 5. Facilities involved in the manufacture of COMIRNATY

Name/address	FEI Number	DUNS number	Inspection/ waiver	Results/ Justification
Pfizer Inc. 875 Chesterfield Parkway West Chesterfield, MO 63017 (b) (4) Manufacture *Drug Substance* Release and stability testing *Drug Product* Release and stability testing	1940118	004954111	Waiver	ORA Surveillance August 19-20, 2019 NAI
Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC 1 Burtt Road Andover, MA 01810 *Drug Substance* Manufacture, release and stability testing *Drug Product* Release and stability testing	1222181	174350868	Pre-License Inspection	CBER Pre-license inspection July 19-23, 2021 VAI
Pharmacia & Upjohn Company LLC 7000 Portage Road Kalamazoo, MI 49001 *Drug Product* LNP production, bulk drug product formulation, fill and finish, primary packaging, secondary packaging, release and stability testing	1810189	618054084	Waiver	ORA/OBPO Surveillance May 11-20, 2021 VAI
Pfizer Manufacturing Belgium NV Rijksweg 12 Puurs, 2870 Belgium *Drug Product* LNP production, bulk drug product formulation, fill and finish, primary packaging, secondary packaging, release and stability testing	1000654629	370156507	Pre-license inspection	CBER Pre-license inspection June 24-July 2, 2021 NAI

Name/address	FEI Number	DUNS number	Inspection/ waiver	Results/ Justification
Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22 Ireland *Drug Product* Release and stability testing	3004145594	985586408	Waiver	ORA Surveillance November 4-12, 2019 VAI
(b) (4) *Drug Product* Release testing (sterility)	(b) (4)	(b) (4)	Waiver	CDER Pre-approval inspection (b) (4) VAI
(b) (4) *Drug Product* Release testing (sterility)	(b) (4)	(b) (4)	Waiver	ORA Surveillance (b) (4) VAI

ORA conducted a surveillance inspection of Pfizer Inc., Chesterfield, MO, from August 19 – 20, 2019. No Form FDA 483 was issued, and the inspection was classified as No Action Indicated (NAI).

CBER conducted a pre-license inspection (PLI) of Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC from July 19 – 23, 2021. All inspectional issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

ORA conducted a surveillance inspection of Pharmacia & Upjohn Company LLC from May 11 – 20, 2021. All inspectional issues were resolved, and the inspection was classified as VAI.

CBER conducted a PLI of Pfizer Manufacturing Belgium NV from June 24 - July 2, 2021. No Form FDA 483 was issued, and the inspection was classified as NAI.

ORA conducted a surveillance inspection of Pfizer Ireland Pharmaceuticals from November 4 – 12, 2019. All inspectional issues were resolved, and the inspection was classified as VAI.

CDER conducted a pre-approval inspection of (b) (4) from (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

ORA conducted a surveillance inspection of (b) (4) from (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The COMIRNATY drug product is filled and stored at -90°C to -60°C in a 2 mL glass vial sealed with a bromobutyl rubber stopper and an aluminum seal with flip-off plastic cap. The glass vials are supplied by (b) (4) The stopper and caps are supplied by (b) (4), respectively.

Pfizer performed container closure integrity testing (CCIT) on the filled 2 mL glass vials using a (b) (4) test method. All acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Nonclinical Toxicology

For the nonclinical safety evaluation, COMIRNATY was evaluated in two repeat dose toxicity studies in Wistar Han rats and a Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) in Wistar Han rats.

The repeat dose toxicity evaluations were conducted on COMIRNATY and a similar vaccine termed BNT162b2 (V8). COMIRNATY and BNT162b2 (V8) have identical amino acid sequences of the encoded antigens but COMIRNATY includes the presence of optimized codons to improve antigen expression. The IM route of exposure was selected as it is the route of clinical administration. Generation of an immune response to COMIRNATY was confirmed in rats in both repeat-dose toxicity studies. In both repeat-dose toxicity studies, administration of COMIRNATY by IM injection to male and female rats once every week for a total of 3 doses was tolerated without evidence of systemic toxicity. Edema and erythema at the injection sites, transient elevation in body temperature, elevations in white blood cells and acute phase reactants and decreased albumin:globulin ratios were observed. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunizations.

For the Combined Fertility and Developmental Study, COMIRNATY was administered to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day). There were some effects (change in body weight and food consumption and effects localized to the injection site) observed in rats in these studies following administration of COMIRNATY that were not considered adverse and a relationship to COMIRNATY was not established. There were no effects on mating performance, fertility, or any ovarian or uterine parameters nor on embryo-fetal or postnatal survival, growth, or development in the offspring. An immune response was observed in female rats following administration of each vaccine candidate and these responses were also detectable in the offspring (fetuses and pups).

Nonclinical Pharmacology and Pharmacokinetics

COMIRNATY was evaluated in nonclinical pharmacology studies using animal models of mice, rats and nonhuman primates (NHP). The data from these studies indicate: (1) strong antigen-binding IgG and high titer neutralizing antibodies in mice, rat and rhesus macaques; (2) Th1-biased CD4+ T-cell response and IFNγ+, CD8+ T-cell response to BNT162b2 in both mouse and NHP studies; and (3) protection of rhesus macaques from an infectious SARS-CoV-2 challenge, with reduced detection of viral RNA in the BNT162b2-immunized animals as compared with the control-immunized macaques.

Nonclinical pharmacokinetics (PK) evaluation included (1) biodistribution of COMIRNATY using (b) (4) expressing RNA as a surrogate reporter in (b) (4) mice and in rats, and (2) the biodistribution and metabolism of the two novel lipids (ALC-0315 and ALC-0159) contained in COMIRNATY in *in vitro* studies and in a PK study in rats following administration of (b) (4) expressing RNA encapsulated in LNPs made with radiolabeled lipid markers. The study results indicate that following IM injection, the RNA encapsulated in LNP mainly localizes to the site of injection and, to a lesser extent, distributes to the liver. The metabolism of ALC-0315 and ALC-0159 was evaluated *in vitro* using blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys and humans and in *vivo* by examining the plasma, urine, feces, and liver samples from the PK study in rats. Approximately 50% of ALC-0159 is excreted unchanged in feces, while metabolism appears to play a role in the elimination of ALC-0315.

5. Clinical Pharmacology

Pharmacodynamic data, comprised of humoral immune responses to COMIRNATY, were obtained in the clinical studies. The data demonstrated that COMIRNATY induces a humoral immune response against the SARS-CoV-2 spike protein. The exact immunologic mechanism that confers protection against SARS-CoV-2 is unknown.

6. Clinical/Statistical

a. Clinical Program

Overview

The Applicant included data from two clinical studies in the BLA. The clinical studies which will be discussed in this SBRA are shown in Table 6.

Table 6. Overview of Clinical Studies

Study ID	**C4591001**	**BNT162-01**
NCT ID	04368728	04380701
Phase	1/2/3	1/2
Countries	Argentina, Brazil, Germany, South Africa, Turkey, U.S.	Germany
Enrollment	Phase 1: 30 participants Phase 2/3: 43,847 participants	24
Age	16 - 85 YOA	18 - 85 YOA
Purpose	Evaluate VE for prevention of COVID-19 (pivotal clinical endpoint study)	Evaluate safety and immunogenicity

Study ID	C4591001	BNT162-01
Control	Saline Placebo	None
Groups	Phase 2/3: 2 groups, randomized 1:1 to receive COMIRNATY or Placebo IM	1 group, randomized received COMIRNATY IM
Schedule	D0, D21	D0, D21
Total follow-up	6 Months (follow-up ongoing)	6 Months (follow-up ongoing)

YOA: years of age; VE: vaccine efficacy; IM: intramuscular; D: day

Study C4591001

Study C4591001 is an ongoing, randomized, placebo-controlled, observer-blind Phase 1/2/3 study being conducted in the U.S., Argentina, Brazil, Germany, South Africa and Turkey. Initially the study was designed as a Phase 1/2 study in healthy adults in the U.S. for vaccine candidate and dosage selection, as well as evaluation of immunogenicity and preliminary efficacy. The protocol was expanded to include a Phase 2/3 portion of the study to evaluate clinical disease efficacy endpoint in individuals 12 years of age and older in the U.S. and additional sites outside of the U.S.

The Phase 1 portion of the study was designed to identify a preferred vaccine candidate, vaccine dose, and administration schedule for further development based on the vaccine's safety, tolerability, and immunogenicity. To this end, two age groups were evaluated in separate cohorts, younger adults 18 through 55 years of age (N=45) and older adults 65 through 85 years of age (N=45). The study population included healthy men and women and excluded participants at high risk of SARS-CoV-2 infection or with serological evidence of prior or current SARS-CoV-2 infection. Two different vaccine candidates were evaluated, and younger participants received increasing dose levels (10, 20 and 30 µg) with progression to higher dose levels in a stepwise manner. Evaluation of increasing doses in the older age group (65 through 85 years) was based on recommendations from an internal review committee that reviewed safety and immunogenicity data derived from adults 18 through 55 years of age. For each vaccine candidate and dose, participants were randomized 4:1, such that 12 participants received the vaccine candidate and 3 participants received placebo. Review of the safety and immunogenicity from the Phase 1 portion of Study C4591001, in combination with data from Study BNT162-01, supported the final vaccine candidate, dose and dosing regimen (BNT162b2 administered at 30 µg, given 3 weeks apart) to proceed to the Phase 2/3 portion of Study C4591001.

In Phase 2/3, participants were enrolled with stratification by age (younger adults: 18 through 55 years of age; older adults: over 55 years of age) with the goal for the older age strata to consist of 40% of the entire study population. Adolescents were added to the protocol, based on review of safety data in younger adults enrolled in the ongoing study; thus, the age strata were revised as follows: 16 through 55 years of age, and 56 years of age and older. The study population for Phase 2/3 includes participants at higher risk for acquiring COVID-19 and at higher risk of severe COVID-19, such as participants working in the healthcare field, participants with autoimmune disease, and participants with chronic but stable medical conditions such as hypertension, asthma, diabetes, and infection with HIV, hepatitis B or hepatitis C. Participants were randomized 1:1 to receive 2 doses of either COMIRNATY or placebo, 3 weeks apart. The Phase 2 portion of the study evaluated reactogenicity and immunogenicity of the vaccine in 360

participants in the early stage of Phase 2/3, and these participants also contribute to the overall efficacy and safety data in the Phase 3 portion.

The ongoing Phase 3 portion of the study is evaluating the safety and efficacy of COMIRNATY for the prevention of COVID-19 occurring at least 7 days after the second dose of vaccine. Efficacy is being assessed throughout a participant's blinded follow-up in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness, an illness visit occurs. Assessments for illness visits include a nasal (mid-turbinate) swab, which is tested at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (i.e., Cepheid; FDA- authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT), to detect SARS-CoV-2. The central laboratory NAAT result is used for the case definition, unless it was not possible to test the sample at the central laboratory. In that case, the following NAAT results are acceptable: Cepheid Xpert Xpress SARS-CoV-2, Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001), and Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001).

The study design included a planned interim analysis of the first primary efficacy endpoint (the efficacy of BNT162b2 against confirmed COVID-19 occurring from 7 days after Dose 2 in participants without evidence of SARS-CoV-2 infection before vaccination) at pre-specified numbers of COVID-19 cases (at least 62, 92, and 120 cases). All primary and secondary efficacy endpoints were analyzed in the final efficacy analysis after at least 164 COVID-19 cases were accrued. Participants are expected to participate for a maximum of approximately 26 months.

Per protocol, since December 14, 2020, following issuance of the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine, study participants 16 years of age and older have been progressively unblinded to their treatment assignment (when eligible per local recommendations) and offered BNT162b2 vaccination if they were randomized to placebo.

The study was unblinded in stages as all ongoing participants were either individually unblinded (when eligible per local recommendations) or the subject had concluded their 6-month post–Dose 2 study visit. Participants 16 years of age and older who participated in the Phase 2/3 study were given the opportunity to receive COMIRNATY no later than the 6-month timepoint after the second study vaccination. Participants who originally received placebo but received COMIRNATY were moved to a new visit schedule to receive both doses of COMIRNATY, 3 weeks apart.

The primary safety and efficacy endpoints were:

1. Primary safety endpoint (descriptive): Solicited local adverse reactions (injection site pain, redness, swelling), solicited systemic adverse events (AE) (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain), unsolicited AEs, serious adverse events (SAEs).

2. First primary efficacy endpoint: COVID-19 incidence per 1000 person-years of follow-up based on laboratory-confirmed NAAT in participants with no serological or virological evidence (up to 7 days after Dose 2) of past SARS-CoV-2 infection.

3. Second primary efficacy endpoint: COVID-19 incidence per 1000 person-years of follow-up based on laboratory-confirmed NAAT in participants with and without serological or virological evidence (up to 7 days after Dose 2) of past SARS-CoV-2 infection.

The pertinent secondary endpoint was:

1. Severe COVID-19 incidence per 1000 person-years of follow-up.

Study C4591001 results

The population in the protocol-specified, event-driven final primary efficacy analysis included all participants 12 years of age and older who had been enrolled from July 27, 2020 and followed for the development of COVID-19 through November 14, 2020. For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0% (95% credible interval: 90.0, 97.9), which met the pre-specified success criterion. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group. This protocol-specified, event-driven final primary efficacy analysis was the basis for issuance of the emergency use authorization for the Pfizer-BioNTech COVID-19 Vaccine on December 11, 2020.

Therefore, the primary study objective of VE against COVID-19 was met as the point estimate was above 50% and the lower bound of the 95% CI of the point estimate of VE was above 30%.

The population for the updated vaccine efficacy analysis per protocol included participants 16 years of age and older who had been enrolled from July 27, 2020, and followed for the development of COVID-19 during blinded placebo-controlled follow-up through March 13, 2021, representing up to ~6 months of follow-up after Dose 2. Overall, 60.8% of participants in the COMIRNATY group and 58.7% of participants in the placebo group had ≥4 months of follow-up time after Dose 2 in the blinded placebo-controlled follow-up period. The overall VE against COVID-19 in participants without evidence of prior SARS-CoV-2 infection was 91.1% (95% CI: 88.8 to 93.1). The overall VE against COVID-19 in participants with or without evidence of prior SARS-CoV-2 infection was 90.9% (95% CI: 88.5 to 92.8).

Subgroup analyses of vaccine efficacy (although limited by small numbers of cases in some subgroups) did not suggest meaningful differences in efficacy across genders, ethnic groups, geographies, or for participants with obesity or medical comorbidities associated with high risk of severe COVID-19.

The updated vaccine efficacy information is presented in Tables 7a and 7b.

Table 7a: First COVID-19 occurrence from 7 days after Dose 2 in participants without evidence of prior SARS-CoV-2 infection - Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period *

Subgroup	COMIRNATY N[a]=19,993 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=20,118 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
All participants	77 6.092 (19,711)	833 5.857 (19,741)	91.1 (88.8, 93.1)
16 through 64 years	70 4.859 (15,519)	709 4.654 (15,515)	90.5 (87.9, 92.7)
65 years and older	7 1.233 (4192)	124 1.202 (4226)	94.5 (88.3, 97.8)

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Table 7b: First COVID-19 occurrence from 7 days after Dose 2 in participants with or without* evidence of prior SARS-CoV-2 infection - Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up Period *

Subgroup	COMIRNATY N[a]=21,047 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a]=21,210 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI[e])
All participants	81 6.340 (20,533)	854 6.110 (20,595)	90.9 (88.5, 92.8)
16 through 64 years	74 5.073 (16,218)	726 4.879 (16,269)	90.2 (87.5, 92.4)
65 years and older	7 1.267 (4315)	128 1.232 (4326)	94.7 (88.7, 97.9)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Efficacy Against Severe COVID-19

Vaccine efficacy against severe COVID-19 for participants with or without prior SARS-CoV-2 infection is shown in Tables 8a and 8b. The VE against severe COVID-19 in participants with or without evidence of prior SARS-CoV-2 infection was 95.3% (95% CI: 71.0 to 99.9) using the protocol definition of severe COVID-19 and 100.0% (95% CI: 87.6 to 100.0) based on the CDC definition of severe COVID-19.

Table 8a: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants 16 Years of Age and Older With or Without* Prior SARS-CoV-2 Infection Based on Protocol† Definition From 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up

	COMIRNATY Cases n1[a] Surveillance Time[b] (n2[c])	Placebo Cases n1[a] Surveillance Time[b] (n2[c])	Vaccine Efficacy % (95% CI[d])
7 days after Dose 2[d]	1 6.353 (20,540)	21 6.237 (20,629)	95.3 (70.9, 99.9)

Table 8b: Vaccine Efficacy – First Severe COVID-19 Occurrence in Participants 16 Years of Age and Older With or Without* Prior SARS-CoV-2 Infection Based on Centers for Disease Control and Prevention (CDC)‡ Definition From 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population During the Placebo-Controlled Follow-up

	COMIRNATY Cases n1[a] Surveillance Time[b] (n2[c])	Placebo Cases n1[a] Surveillance Time[b] (n2[c])	Vaccine Efficacy % (95% CI[d])
7 days after Dose 2[d]	0 6.345 (20,513)	31 6.225 (20,593)	100 (87.6, 100.0)

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

† Severe illness from COVID-19 is defined in the protocol as confirmed COVID-19 and presence of at least 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, saturation of oxygen ≤93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen <300 mm Hg);
- Respiratory failure [defined as needing highflow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an Intensive Care Unit;
- Death.

‡ Severe illness from COVID-19 as defined by CDC is confirmed COVID-19 and presence of at least 1 of the following:

- Hospitalization;
- Admission to the Intensive Care Unit;
- Intubation or mechanical ventilation;
- Death.

a. n1 = Number of participants meeting the endpoint definition.
b. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
c. n2 = Number of participants at risk for the endpoint.

d. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time

Study BNT162-01

Study BNT162-01 is an ongoing Phase 1/2, open-label, dose-finding study to evaluate the safety and immunogenicity of several candidate vaccines, including BNT162b2 (1, 3, 10, 20, and 30 μg), conducted in Germany in healthy and immunocompromised adults. Only safety and immunogenicity data in individuals 16 years of age and older, the population for the intended use and who received the final vaccine formulation (30 μg BNT162b2) are used to support this application. The 30 μg dosage of BNT162b2 was administered to 12 adults 18 to 55 years of age and 12 adults 56 to 85 years of age.

The primary objective was to evaluate the safety of the BNT162 candidate vaccines. Secondary and exploratory objectives were to describe humoral and cellular immune responses following vaccination, measured at baseline and various time points after vaccination, specifically 7 days post Dose 2. Adverse event monitoring was the same as the safety monitoring in study C4591001.

The study started April 23, 2020. The BLA contains safety data (reactogenicity and AE analyses) up to 1 month after Dose 2 (data cutoff date: October 23, 2020), neutralizing antibody data up to ~2 months after Dose 2 (data cutoff date: October 23, 2020), and T-cell data up to ~6 months after Dose 2 (data cutoff date: March 2, 2021).

Study BNT162-01 Results

Disposition of 30 μg BNT162b2 group:

- Safety: Of a total of 24 participants, 12 participants 18 to 55 years of age and 12 participants 56 to 85 years of age completed the visit at 1- month post-Dose 2.
- Immunogenicity: Of the 12 participants, serum neutralizing antibody and T-cell responses were available for 10 and 12 participants, respectively.

Safety: The safety profiles for adult participants 18-55 and 56-85 years of age receiving 30 μg BNT162b2 in this study were similar to age-matched participants in study C4591001.

Immunogenicity: Dose-dependent increases were noted 42 days after Dose 2, compared to SARS-CoV-2 neutralizing GMTs at baseline (pre-Dose 1), and most pronounced at the 30 μg dose level. The Th1 polarization of the T-helper response was indicated by IFNγ and IL-2 production, and only minimal IL-4 production upon antigen-specific (SARS-CoV-2 S protein peptide pools) re-stimulation.

Review of the safety and immunogenicity from Phase 1 part of Study C4591001, in combination with data from Study BNT162-01, supported selection of the final vaccine candidate and dose level (BNT162b2 at 30 μg, given as two doses 3 weeks apart) to proceed into Phase 2/3 part of Study C4591001.

Lot Consistency

Consistency of process performance qualification (PPQ) batches manufactured at both Pfizer Puurs and Pfizer Kalamazoo was demonstrated by verifying process parameters and in-process testing results as well as DP release testing. Data obtained from the analytical comparability assessments on the PPQ batches manufactured at both sites

provide evidence of reproducible and consistent manufacture of COMIRNATY DP of acceptable product quality across all supply nodes.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

BIMO inspection assignments were issued for a total of nine (9) clinical study sites that participated in the conduct of study Protocol C4591001. Three (3) of these inspection assignments focused on clinical study sites that enrolled the pediatric population and six (6) of the study sites enrolled the adult population. The inspections did not reveal findings that impact the BLA.

c. Pediatrics

The Applicant's Pediatric Plan was presented to the FDA Pediatric Review Committee (PeRC) on August 3, 2021. The committee agreed with the Applicant's request for a deferral for studies in participants 0 to <16 years of age because the biological product is ready for approval for use in individuals 16 years of age and older before pediatric studies in participants 0 to <16 years of age are completed (Section 505B(a)(3)(A)(i) of PREA).

The PREA-required studies specified in the approval letter and agreed upon with the Applicant are as follows:

1. Study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age

2. Study C4591007 to evaluate the safety and effectiveness of COMIRNATY in children 6 months to <12 years of age

3. Study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age

7. Safety and Pharmacovigilance

The most commonly reported (≥10%) solicited adverse reactions in COMIRNATY recipients 16 through 55 years of age following any dose were pain at the injection site (88.6%), fatigue (70.1%), headache (64.9%), muscle pain (45.5%), chills (41.5%), joint pain (27.5%), fever (17.8%), and injection site swelling (10.6%). The most commonly reported (≥10%) solicited adverse reactions in COMIRNATY recipients 56 years of age and older following any dose were pain at the injection site (78.2%), fatigue (56.9%), headache, (45.9%), muscle pain (32.5%), chills (24.8%), joint pain (21.5%), injection site swelling (11.8%), fever (11.5%), and injection site redness (10.4%).

Among participants 16 through 55 years of age who had received at least 1 dose of COMIRNATY (N=12,995) or placebo (N=13,026), serious adverse events from Dose 1 up to the participant unblinding date in ongoing follow-up were reported by 103 (0.8%) COMIRNATY recipients and 117 (0.9%) placebo recipients. In a similar analysis in participants 56 years of age and older (COMIRNATY=8,931, placebo=8,895), serious adverse events were reported by 165 (1.8%) COMIRNATY recipients and 151 (1.7%) placebo recipients who received at least 1 dose of COMIRNATY or placebo, respectively. In these analyses, 58.2% of study participants had at least 4 months of

follow-up after Dose 2. There were no notable patterns between treatment groups for specific categories of serious adverse events (including neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY.

From Dose 1 through the March 13, 2021 data cutoff date, there were a total of 38 deaths, 21 in the COMIRNATY group and 17 in the placebo group. None of the deaths were considered related to vaccination.

Since the issuance of the EUA (December 11, 2020), post-authorization safety data has been reported from individuals 16 years of age and older following any dose of COMIRNATY. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Below are presented adverse reactions categorized as important identified risks in the pharmacovigilance plan that have occurred during the conduct of the clinical trial and have been reported following the issuance of the EUA.

Myocarditis/Pericarditis

During the time from Dose 1 to unblinding in Study C4591001, one report of pericarditis was identified in the COMIRNATY group, occurring in a male participant ≥55 years of age, with no medical history, 28 days after Dose 2; the event was assessed by the investigator as not related to the study intervention and was ongoing at the time of the data cutoff. One report of myocarditis was identified in a male participant <55 years of age in the placebo group, occurring 5 days after his second placebo dose.

Post-EUA safety surveillance reports received by FDA and CDC identified serious risks for myocarditis and pericarditis following administration of COMIRNATY. Reporting rates for medical chart-confirmed myocarditis/pericarditis in VAERS have been higher among males under 40 years of age than among females and older males and have been highest in males 12-17 years of age (65 cases per million doses administered as per CDC communication on August 20, 2021), particularly following the second dose, and onset of symptoms within 7 days following vaccination. Although some cases of vaccine-associated myocarditis/pericarditis required intensive care support, available data from short-term follow up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae and outcomes in affected individuals. A mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established.

These safety findings of increased risk for myocarditis/pericarditis led to warning in section 5.2 Warning and Precautions of the PI.

Myocarditis and pericarditis are considered important identified risks in the pharmacovigilance plan included in the BLA. Of note, the Applicant will be required to conduct postmarketing requirement (PMR) safety studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis as well as an unexpected serious risk for subclinical myocarditis (see Section 11c Recommendation for Postmarketing Activities, for study details).

Moreover, since vaccine-associated myocarditis/pericarditis is the most clinically significant identified risk, FDA undertook a quantitative benefit-risk assessment to model the excess risk of myocarditis/pericarditis vs. the expected benefits of preventing COVID-19 and associated hospitalizations, ICU admissions, and deaths. For estimation of risk, the model took a conservative approach by relying on non-chart-confirmed cases from a US healthcare claims database (OPTUM) that could provide a control group and greater confidence in denominators for vaccine exposures. Thus, the estimates of excess risk in this model are higher than the rates estimated from reports to VAERS (an uncontrolled passive surveillance system), with an estimated excess risk approaching 200 cases per million vaccinated males 16-17 years of age (the age/sex-stratified group with the highest risk). For estimation of benefit, the model output was highly dependent on the assumed COVID-19 incidence, as well as assumptions about vaccine efficacy and duration of protection. The assessment therefore considered a range of scenarios including but not limited to a “most likely” scenario associated with recent Delta variant surge and diminished vaccine effectiveness (70% overall, 80% against COVID-19 hospitalization) compared to that observed in the clinical trial. The “worst-case” scenario with low COVID-19 incidence reflecting the July 2021 nadir and the same somewhat diminished vaccine effectiveness as in the “most likely” scenario.

For males and females 18 years of age and older and for females 16-17 years of age, even before accounting for morbidity prevented from non-hospitalized COVID-19, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under all conditions examined. For males 16-17 years of age, the model predicts that the benefits of prevented COVID-19 hospitalizations, ICU admissions and deaths would clearly outweigh the predicted excess risk of vaccine-associated myocarditis/pericarditis under the “most likely” scenario, but that predicted excess cases of vaccine-associated myocarditis/pericarditis would exceed COVID-19 hospitalizations and deaths under the “worst case” scenario. However, this predicted numerical imbalance does not account for the greater severity and length of hospitalization, on average, for COVID-19 compared with vaccine-associated myocarditis/pericarditis. Additionally, the “worst case” scenario model predicts prevention of >13,000 cases of non-hospitalized COVID-19 per million vaccinated males 16-17 years of age, which would include prevention of clinically significant morbidity and/or long-term sequelae associated with some of these cases. Finally, the model does not account for indirect societal/public health benefits of vaccination. Considering these additional factors, FDA concluded that even under the “worst case” scenario the benefits of vaccination sufficiently outweigh risks to support approval of the vaccine in males 16-17 years of age.

Mitigation of the observed risks and associated uncertainties will be accomplished through labeling (including warning statements) and through continued safety surveillance and postmarketing studies to further assess and understand these risks, including an immunogenicity and safety study of lower dose levels of COMIRNATY in individuals 12 through <30 years of age. The Applicant will be required to conduct postmarketing requirement (PMR) safety studies under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the known serious risks of myocarditis and pericarditis and an unexpected serious risk for subclinical myocarditis (see section 11c for study details).

Anaphylaxis
The risk of anaphylaxis was recognized early in the post-authorization time period and it is included as an important identified risk in the PVP. The estimated crude reporting rate for anaphylaxis is 6.0 cases per million doses. Therefore, the incidence of anaphylaxis after receipt of COMIRNATY is comparable with those reported after receipt of other vaccines.

There were no reports of anaphylaxis associated with COMIRNATY in clinical study participants through the cutoff date of March 13, 2021.

A contraindication for individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of COMIRNATY is included in section 4 of the PI. Additionally, a warning statement is included in section 5.1 of the PI instructing that "appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of COMIRNATY"

Pharmacovigilance Plan (PVP)
The Applicant's proposed pharmacovigilance plan (version 1.1) includes the following important risks and missing information:

- Important identified risks: Anaphylaxis; Myocarditis and Pericarditis
- Important potential risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
- Missing information: Use in pregnancy and lactation; Vaccine effectiveness; Use in pediatric individuals <12 years of age

In addition to routine pharmacovigilance, the Applicant will conduct the postmarketing studies listed in Section 11c Recommendation for Postmarketing Activities.

Adverse event reporting under 21 CFR 600.80 and the postmarketing studies in Section 11c are adequate to monitor the postmarketing safety for COMIRNATY.

8. Labeling

The proprietary name, COMIRNATY, was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) on July 2, 2021, and found to be acceptable. CBER communicated this decision to the Applicant on July 6, 2021. The APLB found the PI and package/container labels to be acceptable from a promotional and comprehension perspective. The Review Committee negotiated revisions to the PI, including modifying the proposed proper name from "COVID-19 mRNA vaccine (nucleoside-modified)" to "COVID-19 Vaccine, mRNA" and including a warning for an increased risk of myocarditis and pericarditis following administration of COMIRNATY. All labeling issues regarding the PI and the carton and container labels were acceptably resolved after exchange of information and discussions with the Applicant.

9. Advisory Committee Meetings

Vaccines and Related Biological Products Committee (VRBPAC) meetings were convened on October 22, 2020 to discuss, in general, development for EUA and licensure of vaccines to prevent COVID-19 and on December 10, 2020, to discuss BioNTech Manufacturing GmbH/Pfizer's EUA request for the Pfizer-BioNTech COVID-19 Vaccine.

On October 22, 2020, the VRBPAC was presented with the following items for discussion (no vote):

1. Please discuss FDA's approach to safety and effectiveness data as outlined in the respective guidance documents.

2. Please discuss considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine.

3. Please discuss studies following licensure and/or issuance of an EUA for COVID-19 vaccines to
    a. Further evaluate safety, effectiveness and immune markers of protection
    b. Evaluate the safety and effectiveness in specific populations

In general, the VRBPAC endorsed FDA's approach and recommendations on the safety and effectiveness data necessary to support a BLA and EUA for COVID-19 vaccines as outlined in the respective guidance documents. VRBPAC members recommended for the median follow-up of 2 month to be the minimum follow-up period and suggested longer follow-up periods to evaluate, both safety and efficacy, if feasible. The VRBPAC endorsed the importance of additional studies to further evaluate safety and effectiveness of the vaccine after EUA issuance and/or licensure and underscored the need to evaluate the safety and effectiveness of COVID-19 vaccines in specific populations.

On December 10, 2020, VRBPAC discussed Pfizer- BioNTech Manufacturing GmbH's EUA request for their vaccine to prevent COVID-19 in individuals 16 years of age and older. The committee discussed the safety and efficacy data derived from the clinical disease endpoint efficacy study C4591001.

The VRPBAC voted on one question:

1. Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older?

    The results of the vote were as follows:
    Yes = 17 No = 4 Abstain = 1

The VRBPAC was presented with the following items for discussion (no vote):

1. Pfizer has proposed a plan for continuation of blinded, placebo-controlled follow-up in ongoing trials if the vaccine were made available under EUA. Please discuss

Pfizer's plan, including how loss of blinded, placebo-controlled follow-up in ongoing trials should be addressed.

2. Please discuss any gaps in plans described today and in the briefing documents for further evaluation of vaccine safety and effectiveness in populations who receive the Pfizer-BioNTech COVID-19 Vaccine under an EUA.

The committee discussed potential implications of loss of blinded, placebo-controlled follow-up in ongoing trials including how this may impact availability of safety data to support a BLA. The VRBPAC commented on the need to further assess vaccine effect on asymptomatic infection and viral shedding, and further evaluation of safety and effectiveness in subpopulations such as HIV-infected individuals, individuals with prior exposure to SARS-CoV-2.

FDA did not refer this application to the VRBPAC because our review of the information submitted to this BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

a. Identification of BLA Lots

Upon CBER's request inquiring about what BLA-compliant EUA-labeled lots may be available for use upon licensure of COMIRNATY, the Applicant submitted information listing which lots they considered to be manufactured according to the BLA. To address the issue of these lots not bearing the vial label associated with BLA approval, CBER worked with the Applicant to develop a Dear HCP letter to be included with lots considered by CBER to be BLA-compliant. This letter explained that some lots labeled for EUA use were also considered BLA-compliant and refers HCP to a website for additional information. CBER requested and the Applicant agreed that only EUA-labeled lots that had also undergone CBER lot release according to the BLA would be considered BLA-compliant and listed at the website included in the Dear HCP letter.

b. Exception to the 21 CFR 610.15(a) Requirement for a Preservative

Under 21 CFR 610.15(a), a vaccine product in multiple-dose containers must (absent certain exceptions) contain a preservative. The Applicant submitted a request for exception to this requirement and provided a justification for the multi-dose presentation of COMIRNATY not containing a preservative. CBER considered the Applicant's request for an exception to the 21 CFR 610.15(a) for COMIRNATY as a multiple dose preservative-free presentation acceptable.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, pre-clinical, and product-related data submitted in the original BLA, the Review Committee recommends approval of COMIRNATY for the labeled indication and usage.

b. Benefit/Risk Assessment

Considering the data submitted to support the safety and effectiveness of COMIRNATY that have been presented and discussed in this document, as well as the seriousness of COVID-19, the Review Committee is in agreement that the risk/benefit balance for COMIRNATY is favorable and supports approval for use in individuals 16 years of age and older.

c. Recommendation for Postmarketing Activities

BioNTech Manufacturing GmbH has committed to conduct the following postmarketing activities, which will be included in the approval letter.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

1. Study C4591009, entitled "A Non-Interventional Post-Approval Safety Study of the Pfizer-BioNTech COVID-19 mRNA Vaccine in the United States," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY

   Final Protocol Submission: August 31, 2021
   Monitoring Report Submission: October 31, 2022
   Interim Report Submission: October 31, 2023
   Study Completion: June 30, 2025
   Final Report Submission: October 31, 2025

2. Study C4591021, entitled "Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine," to evaluate the occurrence of myocarditis and pericarditis following administration of COMIRNATY

   Final Protocol Submission: August 11, 2021
   Progress Report Submission: September 30, 2021
   Interim Report 1 Submission: March 31, 2022
   Interim Report 2 Submission: September 30, 2022
   Interim Report 3 Submission: March 31, 2023
   Interim Report 4 Submission: September 30, 2023
   Interim Report 5 Submission: March 31, 2024
   Study Completion: March 31, 2024
   Final Report Submission: September 30, 2024

3. Study C4591021 substudy to describe the natural history of myocarditis and pericarditis following administration of COMIRNATY

   Final Protocol Submission: January 31, 2022
   Study Completion: March 31, 2024
   Final Report Submission: September 30, 2024

4. Study C4591036, a prospective cohort study with at least 5 years of follow-up for potential long-term sequelae of myocarditis after vaccination (in collaboration with Pediatric Heart Network)

Final Protocol Submission: November 30, 2021
Study Completion: December 31, 2026
Final Report Submission: May 31, 2027

5. Study C4591007 substudy to prospectively assess the incidence of subclinical myocarditis following administration of the second dose of COMIRNATY in a subset of participants 5 through 15 years of age

   Final Protocol Submission: September 30, 2021
   Study Completion: November 30, 2023
   Final Report Submission: May 31, 2024

6. Study C4591031 substudy to prospectively assess the incidence of subclinical myocarditis following administration of a third dose of COMIRNATY in a subset of participants 16 to 30 years of age

   Final Protocol Submission: November 30, 2021
   Study Completion: June 30, 2022
   Final Report Submission: December 31, 2022

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

7. Study C4591022, entitled “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)/MotherToBaby Pregnancy Registry”

   Final Protocol Submission: July 1, 2021
   Study Completion: June 1, 2025
   Final Report Submission: December 1, 2025

8. Study C4591007 substudy to evaluate the immunogenicity and safety of lower dose levels of COMIRNATY in individuals 12 through <30 years of age

   Final Protocol Submission: September 30, 2021
   Study Completion: November 30, 2023
   Final Report Submission: May 31, 2024

9. Study C4591012, entitled “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”

   Final Protocol Submission: January 29, 2021
   Study Completion: June 30, 2023
   Final Report Submission: December 31, 2023

10. Study C4591014, entitled “Pfizer-BioNTech COVID-19 BNT162b2 Vaccine Effectiveness Study - Kaiser Permanente Southern California”

Final Protocol Submission: March 22, 2021
Study Completion: December 31, 2022
Final Report Submission: June 30, 2023

PEDIATRIC REQUIREMENTS

11. Deferred pediatric study C4591001 to evaluate the safety and effectiveness of COMIRNATY in children 12 years through 15 years of age

    Final Protocol Submission: October 7, 2020
    Study Completion: May 31, 2023
    Final Report Submission: October 31, 2023

12. Deferred pediatric study C4591007 to evaluate the safety and effectiveness of COMIRNATY in children 6 months to <12 years of age

    Final Protocol Submission: February 8, 2021
    Study Completion: November 30, 2023
    Final Report Submission: May 31, 2024

13. Deferred pediatric study C4591023 to evaluate the safety and effectiveness of COMIRNATY in infants <6 months of age

    Final Protocol Submission: January 31, 2022
    Study Completion: July 31, 2024
    Final Report Submission: October 31, 2024

Marks Decl. Exhibit D

Contains Nonbinding Recommendations

Development and Licensure of Vaccines to Prevent COVID-19

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
June 2020

Preface

Public Comment

This guidance is being issued to address the coronavirus disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket FDA-2020-D-1137 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders, the FDA webpage titled "Search for FDA Guidance Documents," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents, and the FDA webpage titled "Biologics Guidances," *available at* https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances. You may also send an email request to ocod@fda.hhs.gov to receive an additional copy of the guidance. Please include the docket number FDA-2020-D-1137 and complete title of the guidance in the request.

Questions

For questions about this document, contact the Office of Communication, Outreach, and Development (OCOD) by email at ocod@fda.hhs.gov or at 800-835-4709 or 240-402-8010.

Contains Nonbinding Recommendations

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Development and Licensure of Vaccines to Prevent COVID-19

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic which has been caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to assist sponsors in the clinical development and licensure of vaccines for the prevention of COVID-19.

This guidance is intended to remain in effect for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)(2)). The recommendations described in the guidance are expected to assist the Agency and sponsors in the clinical development and licensure of vaccines for the prevention of COVID-19 and reflect the Agency's current thinking on this issue.

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020, titled "Process for Making Available Guidance Documents Related to Coronavirus Disease 2019" (85 FR 16949), *available at* https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), (21 U.S.C. 371(h)(1)(C)), and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices. However, FDA expects that the recommendations set forth in this revised guidance will continue to apply outside the context of the current public health emergency.

Therefore, within 60 days following the termination of the public health emergency, FDA intends to revise and replace this guidance with an updated guidance that incorporates any appropriate changes based on comments received on this guidance and the Agency's experience with implementation.

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "COVID-19." On January 31, 2020, the Secretary of HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.[1] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[2]

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health. There are currently no FDA-licensed vaccines to prevent COVID-19. Commercial vaccine manufacturers and other entities are developing COVID-19 vaccine candidates using different technologies including RNA, DNA, protein, and viral vectored vaccines.

This guidance describes FDA's current recommendations regarding the data needed to facilitate clinical development and licensure of vaccines to prevent COVID-19. There are currently no accepted surrogate endpoints that are reasonably likely to predict clinical benefit of a COVID-19 vaccine. Thus, at this time, the goal of development programs should be to pursue traditional approval via direct evidence of vaccine safety and efficacy in protecting humans from SARS-CoV-2 infection and/or clinical disease.

This guidance provides an overview of key considerations to satisfy regulatory requirements set forth in the investigational new drug application (IND) regulations in 21 CFR Part 312 and licensing regulations in 21 CFR Part 601 for chemistry, manufacturing, and controls (CMC), and nonclinical and clinical data through development and licensure, and for post-licensure safety evaluation of COVID-19 preventive vaccines.[3] FDA is committed to supporting all scientifically sound approaches to attenuating the clinical impact of COVID-19. Sponsors engaged in the development of vaccines to prevent COVID-19 should also see the guidance for industry and investigators, *COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products* (Ref. 1).

[1] Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Jan. 31, 2020, renewed April 21, 2020), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.
[2] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), *available at* https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.
[3] Novel devices used to administer COVID-19 vaccines raise additional issues which are not addressed in this guidance.

There are many COVID-19 vaccines currently in development and FDA recognizes that the considerations presented here do not represent all the considerations necessary to satisfy statutory and regulatory requirements applicable to the licensure of vaccines intended to prevent COVID-19. The nature of a particular vaccine and its intended use may impact specific data needs. We encourage sponsors to contact the Center for Biologics Evaluation and Research (CBER) Office of Vaccines Research and Review (OVRR) with specific questions.

III. CHEMISTRY, MANUFACTURING, AND CONTROLS – KEY CONSIDERATIONS

A. General Considerations

- COVID-19 vaccines licensed in the United States must meet the statutory and regulatory requirements for vaccine development and approval, including for quality, development, manufacture, and control (section 351(a) of the Public Health Service Act (PHS Act), (42 U.S.C. 262)). The vaccine product must be adequately characterized and its manufacture in compliance with applicable standards including current good manufacturing practice (cGMP) (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and 21 CFR Parts 210, 211, and 610). It is critical that vaccine production processes for each vaccine are well defined and appropriately controlled to ensure consistency in manufacturing.

- COVID-19 vaccine development may be accelerated based on knowledge gained from similar products manufactured with the same well-characterized platform technology, to the extent legally and scientifically permissible. Similarly, with appropriate justification, some aspects of manufacture and control may be based on the vaccine platform, and in some instances, reduce the need for product-specific data. FDA recommends that vaccine manufacturers engage in early communications with OVRR to discuss the type and extent of chemistry, manufacturing, and control information needed for development and licensure of their COVID-19 vaccine.

B. Manufacture of Drug Substance and Drug Product

- Data should be provided to show that all source material used in manufacturing is adequately controlled, including, for example, history and qualification of cell banks, history and qualification of virus banks, and identification of all animal derived materials used for cell culture and virus growth.

- Complete details of the manufacturing process must be provided in a Biologics License Application (BLA) to support licensure of a COVID-19 vaccine (21 CFR 601.2). Accordingly, sponsors should submit data and information identifying critical process parameters, critical quality attributes, batch records, defined hold times, and the in-process testing scheme. Specifications should be established for

each critical parameter. Validation data from the manufacture of platform-related products may provide useful supportive information, particularly in the identification of critical parameters.

- In-process control tests must be established that allow quality to be monitored for each lot for all stages of production (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable, 21 CFR 211.110(a)).

- Data to support the consistency of the manufacturing process should be provided, including process validation protocols and study reports, data from engineering lots, and drug substance process performance qualification.

- The manufacturing process must be adequately validated (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable, 21 CFR 211.100(a) and 211.110). Validation would typically include a sufficient number of commercial-scale batches that can be manufactured routinely, meeting predetermined in-process controls, critical process parameters, and lot release specifications. Typically, data on the manufacture of at least three commercial-scale batches are sufficient to support the validation of the manufacturing process (Ref. 2).

- A quality control system should be in place for all stages of manufacturing, including a well-defined testing program to ensure in process/intermediate product quality and product quality throughout the formulation and filling process. This system should also include a well-defined testing program to ensure drug substance quality profile and drug product quality for release. Data on the qualification/validation for all quality indicating assays should be submitted to the BLA to support licensure.

- All quality-control release tests, including key tests for vaccine purity, identity and potency, should be validated and shown to be suitable for the intended purpose. Release specifications are product specific and will be discussed with the sponsor as part of the review of a BLA.

- If adequately justified, final validation of formulation and filling operations may be completed after product approval if the impact on product quality is not compromised. It is important that any data that will be submitted after product approval be agreed upon prior to licensure and be submitted as a postmarketing commitment using the appropriate submission category.

- For vaccine licensure, the stability and expiry date of the vaccine in its final container, when maintained at the recommended storage temperature, should be demonstrated using final containers from at least three final lots made from different vaccine bulks.

- Storage conditions, including container closure integrity, must be fully validated (21 CFR 211.166).

- The vaccine must have been shown to maintain its potency for a period equal to that from the date of release to the expiry date (21 CFR 601.2 and 610.10). Post marketing commitments to provide full shelf life data may be acceptable with appropriate justification.

- A product specific stability program should be established to verify that licensed product maintains quality over the defined shelf life.

C. Facilities and Inspections

- Facilities must be of suitable size and construction to facilitate operations and should be adequately designed to prevent contamination, cross-contamination and mix-ups (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable,21 CFR 211.42(a)). All utilities (including plumbing and sanitation) must be validated, and HVAC systems must provide adequate control over air pressure, micro-organisms, dust, humidity, and temperature, and sufficient protection or containment as needed (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable, 21 CFR 211.46(c)) (Ref. 3). Facility and equipment cleaning and maintenance processes must be developed and validated (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable, 21 CFR 211.56(c) and 211.67(b)).

- Manufacturing equipment should be qualified and sterile filtration and sterilization processes validated. Aseptic processes should be adequately validated using media simulations and personnel should be trained and qualified for their intended duties.

- A quality control unit must be established and must have the responsibility for oversight of manufacturing, and review and release of components, containers and closures, labeling, in-process material, and final products (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and, as applicable, 21 CFR 211.22). The quality control unit must have the responsibility for approving validation protocols, reports, investigate deviations, and institute corrective and preventive actions.

- FDA recommends that vaccine manufacturers engage in early communication with CBER's Office of Compliance and Biologics Quality, Division of Manufacturing and Product Quality to discuss facility preparation and inspection timing.

- Pre-license inspections of manufacturing sites are considered part of the review of a BLA and are generally conducted following the acceptance of a BLA filing (21 CFR 601.20). During the COVID-19 public health emergency, FDA is utilizing all available tools and sources of information to support regulatory decisions on applications that include sites impacted by FDA's ability to inspect due to COVID-19. During this interim period, we are using additional tools, where available, to determine the need for an on-site inspection and to support the

application assessment, such as reviewing a firm's previous compliance history, and requesting records in advance of or in lieu of on-site inspections or voluntarily from facilities and sites.

IV. NONCLINICAL DATA – KEY CONSIDERATIONS

A. General Considerations

- The purpose of nonclinical studies of a COVID-19 vaccine candidate is to define its immunogenicity and safety characteristics through *in vitro* and *in vivo* testing. Nonclinical studies in animal models[4] help identify potential vaccine related safety risks and guide the selection of dose, dosing regimen, and route of administration to be used in clinical studies. The extent of nonclinical data required to support proceeding to first in human (FIH) clinical trials depends on the vaccine construct, the supportive data available for the construct and data from closely related vaccines.

- Data from studies in animal models administered certain vaccine constructs against other coronaviruses (SARS-CoV and MERS-CoV) have raised concerns of a theoretical risk for COVID-19 vaccine-associated enhanced respiratory disease (ERD). In these studies, animal models were administered vaccine constructs against other coronaviruses and subsequently challenged with the respective wild-type virus. These studies have shown evidence of immunopathologic lung reactions characteristic of a Th-2 type hypersensitivity similar to ERD described in infants and animals that were administered formalin-inactivated respiratory syncytial virus (RSV) vaccine and that were subsequently challenged with RSV virus due to natural exposure or in the laboratory, respectively (Refs. 4-9). Vaccine candidates should be assessed in light of these studies as described in section D, below.

- FDA recommends that vaccine manufacturers engage in early communications with FDA to discuss the type and extent of nonclinical testing required for the particular COVID-19 vaccine candidate to support proceeding to FIH clinical trials and further clinical development.

B. Toxicity Studies (Refs. 10-14)

- For a COVID-19 vaccine candidate consisting of a novel product type and for which no prior nonclinical and clinical data are available, nonclinical safety studies will be required prior to proceeding to FIH clinical trials 21 CFR 312.23(a)(8).

[4] The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design. We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. Proposals, with justification for any potential alternative approaches (e.g., in vitro or in silico testing), should be submitted during early communication meetings with FDA (see section VI of this document). We will consider if such an alternative method could be used in place of an animal test method.

- In some cases, it may not be necessary to perform nonclinical safety studies prior to FIH clinical trials because adequate information to characterize product safety may be available from other sources. For example, if the COVID-19 vaccine candidate is made using a platform technology utilized to manufacture a licensed vaccine or other previously studied investigational vaccines and is sufficiently characterized, it may be possible to use toxicology data (e.g., data from repeat dose toxicity studies, biodistribution studies) and clinical data accrued with other products using the same platform to support FIH clinical trials for that COVID-19 vaccine candidate. Vaccine manufacturers should summarize the findings and provide a rationale if considering using these data in lieu of performing nonclinical safety studies.

- When needed to support proceeding to FIH clinical trials, nonclinical safety assessments including toxicity and local tolerance studies must be conducted under conditions consistent with regulations prescribing good laboratory practices for conducting nonclincial laboratory studies (GLP) (21 CFR Part 58). Such studies should be completed and analysed prior to initiation of FIH clinical trials. When toxicology studies do not adequately characterize risk, additional safety testing should be conducted as appropriate.

- Data from toxicity studies may be submitted as unaudited final draft toxicicologic reports to accelerate proceeding to FIH clincial trials with COVID-19 vaccine candidates. The final, fully quality-assured reports should be available to FDA within 120 days of the start of the FIH clinical trial.

- Use of COVID-19 preventive vaccines in pregnancy and in women of childbearing potential will be an important consideration for vaccination programs. Therefore, FDA recommends that prior to enrolling pregnant women and women of childbearing potential who are not actively avoiding pregnancy in clinical trials, sponsors conduct developmental and reproductive toxicity (DART) studies with their respective COVID-19 vaccine candidate. Alternatively, sponsors may submit available data from DART studies with a similar product using comparable platform technology if, after consultation with the agency, the agency agrees those data are scientifically sufficient.

- Biodistribution studies in an animal species should be considered if the vaccine construct is novel in nature and there are no existing biodistribution data from the platform technology. These studies should be conducted if there is a likelihood of altered infectivity and tissue tropism or if a novel route of administration and formulation is to be used.

C. Characterization of the Immune Response in Animal Models

- Immunogenicity studies in animal models responsive to the selected COVID-19 vaccine antigen should be conducted to evaluate the immunologic properties of the COVID-19 vaccine candidate and to support FIH clinical trials. The aspects of

immunogenicity to be measured should be appropriate for the vaccine construct and its intended mechanism of action.

- Studies should include an evaluation of humoral, cellular, and functional immune responses, as appropriate to each of the included COVID-19 antigens. Use of antigen-specific enyzme linked immunosorbent assays (ELISA) should be considered to characterize the humoral response. Evaluation of cellular reponses should include the examination of CD8+ and CD4+ T cell responses using sensitive and specific assays. The functional activity of immune responses should be evaluated *in vitro* in neutralization assays using either wild-type virus or pseudovirion virus. The assays used for immunogencity evaluation should be demonstrated to be suitable for their intended purpose.

D. Studies to Address the Potential for Vaccine-associated Enhanced Respiratory Disease

- Current knowledge and understanding of the potential risk of COVID-19 vaccine associated ERD is limited, as is understanding of the value of available animal models in predicting the likelihood of such occurrence in humans. Nevertheless, studies in animal models (e.g., rodents and non-human primates) are considered important to address the potential for vaccine-associated ERD.

- Post-vaccination animal challenge studies and the characterization of the type of the nonclinical and clinical immune response induced by the particular COVID-19 vaccine candidate can be used to evaluate the likelihood of the vaccine to induce vaccine-associated ERD in humans.

- To support proceeding to FIH clinical trials, sponsors should conduct studies characterizing the vaccine-induced immune response in animal models evaluating immune markers of potential ERD outcomes. These should include assessments of functional immune responses (e.g., neutralizing antibody) versus total antibody responses and Th1/Th2 balance in animals vaccinated with clinically relevant doses of the COVID-19 vaccine candidate.

- COVID-19 vaccine candidates with immunogenicity data demonstrating high neutralizing antibody titers and Th1-type T cell polarization may be allowed to proceed to FIH trials without first completing postvaccination challenge studies in appropriate animal models, provided adequate risk mitigation strategies are put in place in the FIH trials. In these situations, postvaccination challenge studies are expected to be conducted in parallel with FIH trials to ensure the potential for vaccine-associated ERD is addressed prior to enrolling large numbers of human subjects into Phase 2 and 3 clinical trials. For COVID-19 vaccine candidates for which other data raise increased concerns about ERD, postvaccination animal challenge data and/or animal immunopathology studies are critical to assess protection and/or ERD *prior* to advancing to FIH clinical trials.

- The totality of data for a specific COVID-19 vaccine candidate, including data from postvaccination challenge studies in small animal models and from FIH clinical trials characterizing the type of immune responses induced by the vaccine will be considered in determining whether Phase 3 studies can proceed in the absence of postvaccination challenge data to address risk of ERD.

V. CLINICAL TRIALS – KEY CONSIDERATIONS

A. General Considerations

- Understanding of SARS-CoV-2 immunology, and specifically vaccine immune responses that might predict protection against COVID-19, is currently limited and evolving. Thus, while evaluation of immunogenicity is an important component of COVID-19 vaccine development, at this time, the goal of development programs should be to pursue traditional approval via direct evidence of vaccine efficacy in protecting humans from SARS-CoV-2 infection and/or disease.

- Clinical development programs for COVID-19 vaccines might be expedited by adaptive and/or seamless clinical trial designs (described below) that allow for selection between vaccine candidates and dosing regimens and for more rapid progression through the usual phases of clinical development.

- Regardless of whether clinical development programs proceed in discrete phases with separate studies or via a more seamless approach, an adequate body of data, including data to inform the risk of vaccine-associated ERD, will be needed as clinical development progresses to support the safety of vaccinating the proposed study populations and number of participants and, for later stage development, to ensure that the study design is adequate to meet its objectives.

- FDA can provide early advice, and potentially concurrence in principle, on plans for expedited/seamless clinical development. However, sponsors should plan to submit summaries of data available at each development milestone for FDA review and concurrence prior to advancing to the next phase of development.

- Conducting clinical trials in the setting of a public health emergency presents operational challenges. FDA has issued guidance to provide general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity for the duration of the COVID-19 public health emergency. It should be noted that not all of the recommendations in that guidance may be applicable to vaccine development, given some of the different considerations for these products (Ref. 15).

B. Trial Populations

- Once acceptable pre-clinical data are available, FIH and other early phase studies (which typically expose 10–100 participants to each vaccine candidate being evaluated) should first enroll healthy adult participants who are at low risk of severe COVID-19. Exclusion of participants at higher risk of severe COVID-19 from early phase studies is necessary to mitigate potential risk of vaccine-associated ERD until additional data to inform that potential risk becomes available through ongoing product development.

    - As the understanding of COVID-19 pathogenesis continues to evolve, exclusion criteria should reflect the current understanding of risk factors for more severe COVID-19, such as those described by the Centers for Disease Control and Prevention (Ref. 16).

    - Older adult participants (e.g., over 55 years of age) may be enrolled in FIH and other early phase studies so long as they do not have medical comorbidities associated with an increased risk of severe COVID-19. Some preliminary safety data in younger adults (e.g., 7 days after a single vaccination) should be available prior to enrolling older adult participants, especially for vaccine platforms without prior clinical experience.

    - If possible, early clinical studies should also exclude participants at high risk of SARS-CoV-2 exposure (e.g., healthcare workers).

- Sponsors should collect and evaluate at least preliminary clinical safety and immunogenicity data for each dose level and age group (e.g., younger versus older adults) to support progression of clinical development to include larger numbers (e.g., hundreds) of participants and participants at higher risk of severe COVID-19.

    - Preliminary immunogenicity data from early phase development should include assessments of neutralizing vs. total antibody responses and Th1 vs. Th2 polarization.

    - Additional data to further inform potential risk of vaccine-associated ERD and to support progression of clinical development, if available, may include preliminary evaluation of COVID-19 disease outcomes from earlier clinical development and results of non-clinical studies evaluating protection and/or histopathological markers of vaccine-associated ERD following SARS-CoV-2 challenge.

- To generate sufficient data to meet the BLA approval standard, late phase clinical trials to demonstrate vaccine efficacy with formal hypothesis testing will likely need to enroll many thousands of participants, including many with medical comorbidities for trials seeking to assess protection against severe COVID-19.

    - Initiation of late phase trials should be preceded by adequate characterization of safety and immunogenicity (e.g., in a few hundred participants for each

vaccine candidate, dose level, and age group to be evaluated) to support general safety, potential for vaccine efficacy, and low risk of vaccine-associated ERD.

- Results of non-clinical studies evaluating protection and/or histopathological markers of vaccine-associated ERD following SARS-CoV-2 challenge and COVID-19 disease outcomes from earlier clinical development are other potentially important sources of information to support clinical trials with thousands of participants.

- Although establishing vaccine safety and efficacy in SARS-CoV-2 naïve individuals is critical, vaccine safety and COVID-19 outcomes in individuals with prior SARS-CoV-2 infection, which might have been asymptomatic, is also important to examine because pre-vaccination screening for prior infection is unlikely to occur in practice with the deployment of licensed COVID-19 vaccines. Therefore, COVID-19 vaccine trials need not screen for or exclude participants with history or laboratory evidence of prior SARS-CoV-2 infection. However, individuals with acute COVID-19 (or other acute infectious illness) should be excluded from COVID-19 vaccine trials.

- FDA encourages the inclusion of diverse populations in all phases of vaccine clinical development. This inclusion helps to ensure that vaccines are safe and effective for everyone in the indicated populations.

  - FDA strongly encourages the enrollment of populations most affected by COVID-19, specifically racial and ethnic minorities.

  - Evaluation of vaccine safety and efficacy in late phase clinical development in adults should include adequate representation of elderly individuals and individuals with medical comorbidities.

  - FDA encourages vaccine developers to consider early in their development programs data that might support inclusion of pregnant women and women of childbearing potential who are not actively avoiding pregnancy in pre-licensure clinical trials (Ref. 17).

  - It is important for developers of COVID-19 vaccines to plan for pediatric assessments of safety and effectiveness, given the nature of the COVID-19 public health emergency, and to help ensure compliance with the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act (21 U.S.C. 355c)) (Ref. 18). The epidemiology and pathogenesis of COVID-19, and the safety and effectiveness of COVID-19 vaccines, may be different in children compared with adults. In order to ensure compliance with 21 CFR Part 50 Subpart D (Additional safeguards for children in clinical investigations), considerations on the prospect of direct benefit and acceptable risk to support initiation of pediatric studies, and the appropriate design and endpoints for pediatric studies, should be discussed in the context of specific vaccine development programs.

C. Trial Design

- Early phase trials often aim to down-select among multiple vaccine candidates and/or dosing regimens via randomization of participants to different treatment groups. While including a placebo control and blinding are not required for early phase studies, doing so may assist in interpretation of preliminary safety data.

- Later phase trials, including efficacy trials, should be randomized, double-blinded, and placebo controlled.

    - An individually randomized controlled trial with 1:1 randomization between vaccine and placebo groups is usually the most efficient study design for demonstrating vaccine efficacy. Other types of randomization, such as cluster randomization, may be acceptable but require careful consideration of potential biases that are usually avoided with individual randomization.

    - An efficacy trial that evaluates multiple vaccine candidates against a single placebo group may be an acceptable approach to further increase efficiency, provided that the trial is adequately designed with appropriate statistical methods to evaluate efficacy.

    - If the availability of a COVID-19 vaccine proven to be safe and effective precludes ethical inclusion of a placebo control group, that vaccine could serve as the control treatment in a study designed to evaluate efficacy with non-inferiority hypothesis testing.

- Protocols for adaptive trials should include pre-specified criteria for adding or removing vaccine candidates or dosing regimens, and protocols for seamless trials should include pre-specified criteria (e.g., safety and immunogenicity data) for advancing from one phase of the study to the next.

- Follow-up of study participants for COVID-19 outcomes (in particular, for severe COVID-19 disease manifestations) should continue as long as feasible, ideally at least one to two years, to assess duration of protection and potential for vaccine-associated ERD as immune responses to the vaccine wane.

- Efficacy trials should include contingency plans for continued follow up and analysis of safety and effectiveness outcomes in the event that a safe and effective vaccine becomes available (e.g., as demonstrated in a planned interim analysis or as demonstrated in another clinical trial). In that case, discussion with the agency may be necessary to address ethical arguments to break the blind and offer vaccine to placebo recipients.

- In cases where statistical equivalency testing of vaccine immune responses in humans is required to support manufacturing consistency (clinical lot-to-lot consistency trial), this testing can be incorporated into the design of an efficacy trial and does not need to be conducted in a separate study.

D. Efficacy Considerations

- Either laboratory-confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection is an acceptable primary endpoint for a COVID-19 vaccine efficacy trial.

  - Acute cases of COVID-19 should be virologically confirmed (e.g., by RT-PCR).

  - SARS-CoV-2 infection, including asymptomatic infection, can be monitored for and confirmed either by virologic methods or by serologic methods evaluating antibodies to SARS-CoV-2 antigens not included in the vaccine.

- Standardization of efficacy endpoints across clinical trials may facilitate comparative evaluation of vaccines for deployment programs, provided that such comparisons are not confounded by differences in trial design or study populations. To this end, FDA recommends that either the primary endpoint or a secondary endpoint (with or without formal hypothesis testing) be defined as virologically confirmed SARS-CoV-2 infection with one or more of the following symptoms:

  - Fever or chills
  - Cough
  - Shortness of breath or difficulty breathing
  - Fatigue
  - Muscle or body aches
  - Headache
  - New loss of taste or smell
  - Sore throat
  - Congestion or runny nose
  - Nausea or vomiting
  - Diarrhea

- As it is possible that a COVID-19 vaccine might be much more effective in preventing severe versus mild COVID-19, sponsors should consider powering efficacy trials for formal hypothesis testing on a severe COVID-19 endpoint. Regardless, severe COVID-19 should be evaluated as a secondary endpoint (with or without formal hypothesis testing) if not evaluated as a primary endpoint. FDA recommends that severe COVID-19 be defined as virologically confirmed SARS-CoV-2 infection with any of the following:

  - Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, $SpO2 \leq 93\%$ on room air at sea level or $PaO2/FiO2 < 300$ mm Hg)
  - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO)
  - Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors)
  - Significant acute renal, hepatic, or neurologic dysfunction

- Admission to an ICU
- Death

- SARS-CoV-2 infection (whether or not symptomatic) should be evaluated as a secondary or exploratory endpoint, if not evaluated as a primary endpoint.

- The above diagnostic criteria may need to be modified in certain populations; for example, in pediatric patients and those with respiratory comorbidities. Sponsors should discuss their proposed case definitions with the Agency prior to initiating enrollment.

E. Statistical Considerations

- To ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%.

  - The same statistical success criterion should be used for any interim analysis designed for early detection of efficacy.

  - A lower bound ≤30% but >0% may be acceptable as a statistical success criterion for a secondary efficacy endpoint, provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint.

- For non-inferiority comparison to a COVID-19 vaccine already proven to be effective, the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary relative efficacy point estimate is >-10%.

- For each vaccine candidate, appropriate statistical methods should be used to control type 1 error for hypothesis testing on multiple endpoints and/or interim efficacy analyses.

- Late phase studies should include interim analyses to assess risk of vaccine-associated ERD (see section F) and futility.

- Study sample sizes and timing of interim analyses should be based on the statistical success criteria for primary and secondary (if applicable) efficacy analyses and realistic, data-driven estimates of vaccine efficacy and incidence of COVID-19 (or SARS-CoV-2 infection) for the populations and locales in which the trial will be conducted.

F. Safety Considerations

- The general safety evaluation of COVID-19 vaccines, including the size of the safety database to support vaccine licensure, should be no different than for other preventive vaccines for infectious diseases. Safety assessments throughout clinical development should include:

  - Solicited local and systemic adverse events for at least 7 days after each study vaccination in an adequate number of study participants to characterize reactogenicity (including at least a subset of participants in late phase efficacy trials).

  - Unsolicited adverse events in all study participants for at least 21–28 days after each study vaccination.

  - Serious and other medically attended adverse events in all study participants for at least 6 months after completion of all study vaccinations. Longer safety monitoring may be warranted for certain vaccine platforms (e.g., those that include novel adjuvants).

  - All pregnancies in study participants for which the date of conception is prior to vaccination or within 30 days after vaccination should be followed for pregnancy outcomes, including pregnancy loss, stillbirth, and congenital anomalies.

- The pre-licensure safety database for preventive vaccines for infectious diseases typically consists of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure. FDA anticipates that adequately powered efficacy trials for COVID-19 vaccines will be of sufficient size to provide an acceptable safety database for each of younger adult and elderly populations, provided that no significant safety concerns arise during clinical development that would warrant further pre-licensure evaluation.

- COVID-19 vaccine trials should periodically monitor for unfavorable imbalances between vaccine and control groups in COVID-19 disease outcomes, in particular for cases of severe COVID-19 that may be a signal for vaccine-associated ERD.

  - Studies should include pre-specified criteria for halting based on signals of potential vaccine-associated ERD.

  - FDA recommends use of an independent data safety monitoring board (DSMB) (Ref. 18) for vaccine-associated ERD and other safety signal monitoring, especially during later stage development.

VI. POST-LICENSURE SAFETY EVALUATION – KEY CONSIDERATIONS

A. General Considerations

- As with all licensed vaccines, there can be limitations in the safety database accrued from the pre-licensure clinical studies of a COVID-19 vaccine. For example:
    - The number of subjects receiving a COVID-19 vaccine in pre-licensure clinical studies may not be adequate to detect some adverse reactions that may occur infrequently.
    - Pre-licensure safety data in some subpopulations likely to receive a COVID-19 vaccine (e.g., pregnant individuals, or individuals with medical comorbidities) may be limited at the time of licensure.
    - For some COVID-19 vaccines, the safety follow-up period to monitor for possible vaccine-associated ERD and other adverse reactions may not have been completed for all subjects enrolled in pre-licensure clinical studies before the vaccine is licensed.

- For COVID-19 vaccines, it is likely that during the early postmarketing period, a large population might be vaccinated in a relatively short timeframe. Thus, FDA recommends early planning of pharmacovigilance activities before licensure.

- To facilitate accurate recording and identification of vaccines in health records, manufacturers should consider establishment of individual Current Procedural Terminology (CPT) codes and the use of bar codes to label the immediate container.

B. Pharmacovigilance Activities for COVID-19 Vaccines

- Routine pharmacovigilance for licensed biological products includes expedited reporting of serious and unexpected adverse events as well as periodic safety reports in accordance with 21 CFR 600.80 (Postmarketing reporting of adverse experiences).

- FDA recommends that at the time of a BLA submission for a COVID-19 vaccine, applicants submit a Pharmacovigilance Plan (PVP) as described in the FDA Guidance for Industry; E2E Pharmacovigilance Planning (Ref. 20). The contents of a PVP for a COVID-19 vaccine will depend on its safety profile and will be based on data, which includes the pre-licensure clinical safety database, preclinical data, and available safety information for related vaccines, among other considerations.

- The PVP should include actions designed to address all important identified risks, important potential risks or important missing information. Pharmacoepidemiologic studies or other actions to evaluate notable potential risks, such as vaccine-associated ERD, should be considered. FDA may recommend one or more of the following as components of a PVP for a COVID-19 vaccine:

- Submission of reports of specific adverse events of interest in an expedited manner beyond routine required reporting;
- Submission of adverse event report summaries at more frequent intervals than specified for routine required reporting;
- Ongoing and/or extended safety follow-up (under an IND) for vaccine-associated ERD of subjects enrolled in pre-licensure clinical studies;
- A pharmacoepidemiologic study to further evaluate (an) important identified or potential risk(s) from the clinical development program, such as vaccine-associated ERD or other uncommon or delayed-onset adverse events of special interest;
- A pregnancy exposure registry that actively collects information on vaccination during pregnancy and associated pregnancy and infant outcomes (Ref. 21).

C. Required Postmarketing Safety Studies

- Section 505(o)(3) of the FD&C Act (21 U.S.C. 355(o)(3)) authorizes FDA to require certain postmarketing studies or clinical trials for prescription drugs approved under section 505(b) of the FD&C Act (21 U.S.C. 355(b)) and biological products approved under section 351 of the PHS Act (42 U.S.C. 262) (Ref. 22). Under section 505(o)(3), FDA can require such studies or trials at the time of approval to assess a known serious risk related to the use of the drug, to assess signals of serious risk related to the use of the drug, or to identify an unexpected serious risk when available data indicate the potential for a serious risk. Under section 505(o)(3), FDA can also require such studies or trials after approval if FDA becomes aware of new safety information, which is defined at section 505-1(b)(3) of the FD&C Act (21 U.S.C. 355-1(b)(3)).

- For COVID-19 vaccines, FDA may require postmarketing studies or trials to assess known or potential serious risks when such studies or trials are warranted.

VII. DIAGNOSTIC AND SEROLOGICAL ASSAYS – KEY CONSIDERATIONS

- Diagnostic assays used to support the pivotal efficacy analysis (e.g., RT-PCR) should be sensitive and accurate for the purpose of confirming infection and should be validated before use.

- Assays used for immunogenicity evaluation should be suitable for their intended purpose of assessing relevant immune responses to vaccination and be validated before use in pivotal clinical trials.

VIII. ADDITIONAL CONSIDERATIONS

A. Additional Considerations in Demonstrating Vaccine Effectiveness

- Given the current state of knowledge about COVID-19, the most direct approach to demonstrate effectiveness for a COVID-19 vaccine candidate is based on clinical endpoint efficacy trials showing protection against disease (see section V. D. above).

- Once additional understanding of SARS-CoV-2 immunology, and specifically vaccine immune responses that might be reasonably likely to predict protection against COVID-19, is acquired, accelerated approval of a COVID-19 vaccine pursuant to section 506 of the FD&C Act (21 U.S.C. 356) and 21 CFR 601.40 may be considered if an applicant provides sufficient data and information to meet the applicable legal requirements. For a COVID-19 vaccine, it may be possible to approve a product under these provisions based on adequate and well-controlled clinical trials establishing an effect of the product on a surrogate endpoint (e.g., immune response) that is reasonably likely to predict clinical benefit.

- A potential surrogate endpoint likely would depend on the characteristics of the vaccine, such as antigen structure, mode of delivery, and antigen processing and presentation in the individual vaccinated. For example, an immune marker established for an adenovirus-based vaccine cannot be presumed applicable to a VSV-based vaccine, given that the two vaccines present antigen in different ways and engender different types of protective immune responses.

- Since SARS-CoV-2 represents a novel pathogen, a surrogate endpoint reasonably likely to predict protection from COVID-19 should ideally be derived from human efficacy studies examining clinical disease endpoints. If the surrogate endpoint is derived from other data sources, sponsors should consult the FDA to reach agreement on the use of the surrogate endpoint.

- An adequate dataset evaluating the safety of the vaccine in humans would need to be provided for consideration of licensure.

- For drugs granted accelerated approval, postmarketing confirmatory trials have been required to verify and describe the predicted effect on clinical benefit. These studies should usually be underway at the time of the accelerated approval, 21 CFR Part 601, Subpart E, and must be completed with due diligence (section 506(c)(3)(A) of the FD&C Act (21 U.S.C. 356(c)(3)(A)) and 21 CFR 601.41).

- If it is no longer possible to demonstrate vaccine effectiveness by way of conducting clinical disease endpoint efficacy studies, the use of a controlled human infection model to obtain evidence to support vaccine efficacy may be considered. However, many issues, including logistical, human subject protection, ethical, and scientific issues, would need to be satisfactorily addressed. At this

time no controlled human infection models for SARS-CoV-2 have been established or characterized.

B. Emergency Use Authorization

- An Emergency Use Authorization (EUA) may be issued only after several statutory requirements are met (section 564 of the FD&C Act (21 U.S.C. 360bbb-2)) (Ref. 23). Among these requirements is a determination by FDA that the known and potential benefits of a product, when used to diagnose, prevent, or treat serious or life-threatening diseases, outweigh the known and potential risks of the product.

- Issuance of an EUA (Ref. 23) may be appropriate for a COVID-19 vaccine provided the standard for issuing an EUA is met. Issuance of an EUA for a COVID-19 vaccine prior to the completion of large randomized clinical efficacy trials could reduce the ability to demonstrate effectiveness of the investigational vaccine in a clinical disease endpoint efficacy trial to support licensure, and such clinical disease endpoint efficacy trials may be needed to investigate the potential for vaccine-associated ERD. Thus, for a vaccine for which there is adequate manufacturing information, issuance of an EUA may be appropriate once studies have demonstrated the safety and effectiveness of the vaccine but before the manufacturer has submitted and/or FDA has completed its formal review of the biologics license application.

- In the case of investigational vaccines being developed for the prevention of COVID-19, any assessment regarding an EUA would be made on a case by case basis considering the target population, the characteristics of the product, the preclinical and human clinical study data on the product, and the totality of the available scientific evidence relevant to the product.

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* When finalized, this guidance will represent FDA's current thinking on this topic.

Marks Decl. Exhibit E

August 23, 2021

Meryl Nass, M.D.
Robert F. Kennedy, Jr.
Children's Health Defense
1227 North Peachtree Parkway
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Peachtree City, GA 30269

Re: Citizen Petition (Docket Number FDA-2021-P-0460)

Dear Dr. Nass and Mr. Kennedy,

This letter responds to the citizen petition dated May 16, 2021 that you submitted to the Food and Drug Administration (FDA, the Agency, we) on behalf of Children's Health Defense (Petitioner) relating to: clinical trials, Emergency Use Authorization, licensure, and advertising and promotion of vaccines to prevent Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (the Petition).

In the Petition, Petitioner requests that FDA:

1. "revoke all EUAs and refrain from approving any future EUA, NDA, or BLA for any COVID vaccine for all demographic groups";
2. "immediately refrain from allowing minors to participate in COVID vaccine trials, refrain from amending EUAs to include children, and immediately revoke all EUAs that permit vaccination of children under 16 for the Pfizer vaccine and under 18 for other COVID vaccines";
3. "immediately revoke tacit approval that pregnant women may receive any EUA or licensed COVID vaccines and immediately issue public guidance to that effect";
4. "immediately amend [FDA's] existing guidance for the use of the chloroquine drugs, ivermectin, and any other drugs demonstrated to be safe and effective against COVID…and immediately issue notifications to all stakeholders";
5. "issue guidance to the Secretary of the Defense [sic] and the President not to grant an unprecedented Presidential waiver of prior consent regarding COVID vaccines for Servicemembers [sic]";
6. "issue guidance…to affirm that all citizens have the option to accept or refuse administration of investigational COVID vaccines without adverse work, educational or other non-health related consequences"; and

7. "[p]ending revocation of COVID vaccine EUAs, FDA should issue guidance that all marketing and promotion of COVID vaccines must refrain from labeling them 'safe and effective.'"

Petition at 1-2.

In this letter, we discuss the safety of licensed and authorized vaccines. We then turn to the requests contained in the Petition. We consider each of your requests in light of the legal standards for FDA action, and provide our conclusions based on the facts, the science, and the law.

This letter responds to the Petition in full. FDA has carefully reviewed the Petition and other relevant information available to the Agency. Based on our review of these materials and for the reasons described below, we conclude that the Petition does not contain facts demonstrating any reasonable grounds for the requested action. In accordance with 21 CFR § 10.30(e)(3), and for the reasons stated below, FDA is denying the Petition.

Here is an outline of our response:

I. Background

There is currently a pandemic of respiratory disease, COVID-19, caused by a novel coronavirus, SARS-CoV-2. The COVID-19 pandemic presents an extraordinary challenge to global health. On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration

of a public health emergency related to COVID-19.[1]On February 4, 2020, pursuant to section 564 of the FD&C Act (21 U.S.C. § 360bbb-3), the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves the virus that causes COVID-19.[2] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic ("COVID-19 EUA Declaration"), pursuant to section 564(b)(1) of the FD&C Act.[3] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[4]

Commercial vaccine manufacturers and other entities are developing COVID-19 vaccine candidates, and clinical studies of these vaccines are underway and/or have been completed. Between December 11, 2020 and February 27, 2021, FDA issued emergency use authorizations for three vaccines to prevent COVID-19, including vaccines sponsored by Pfizer Inc. (Pfizer); ModernaTX, Inc. (Moderna); and Janssen Biotech, Inc. (Janssen), a pharmaceutical company of Johnson & Johnson. FDA received a Biologics License Application (BLA) for the COVID-19 vaccine, BNT162b2, intended to prevent COVID-19 in individuals 16 years of age and older. As announced by FDA on August 23, 2021, the Agency is issuing a biologics license for this COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) to BioNTech Manufacturing GmbH.[5]

II. Vaccines That Are FDA-Licensed or Receive an Emergency Use Authorization Meet Relevant Statutory Requirements

a. Vaccines that are FDA-Licensed are Safe

i. Vaccines that are FDA-Licensed Are Shown to Be Safe at the Time of Licensure

FDA has a stringent regulatory process for licensing vaccines.[6,7] The Public Health Service Act (PHS Act) authorizes FDA to license biological products, including vaccines, if they have

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[1] Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Originally issued on Jan. 31, 2020, and subsequently renewed), https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx

[2] HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.

[3] HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

[4] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak, issued March 13, 2020, https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/ .

[5] BioNTech Manufacturing GmbH is the biologics license holder for this vaccine, which is manufactured by Pfizer Inc. for BioNTech Manufacturing GmbH (hereinafter "BioNTech"). The basis for FDA's licensure decision is set forth in FDA's Summary Basis for Regulatory Action (SBRA) for the BioNTech application. This memorandum will be posted on fda.gov. We incorporate by reference the SBRA for the BLA.

[6] CDC, Ensuring the Safety of Vaccines in the United States, February 2013, https://www.cdc.gov/vaccines/hcp/patient-ed/conversations/downloads/vacsafe-ensuring-bw-office.pdf.

[7] FDA, Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.

been demonstrated to be "safe, pure, and potent."[8] Prior to approval by FDA, vaccines are extensively tested in non-clinical studies and in humans. FDA's regulations describe some of the extensive data and information that each sponsor of a vaccine must submit to FDA in order to demonstrate the product's safety before FDA will consider licensing the vaccine. FDA requires that the sponsor's biologics license application (BLA) include, among other things, data derived from nonclinical and clinical studies showing the product's safety, purity, and potency; a full description of manufacturing methods for the product; data establishing the product's stability through the dating period; and a representative sample of the product and summaries of results of tests performed on the lot(s) represented by the sample.[9]

As is evident from the language of the PHS Act and FDA's regulations, the licensure process for a vaccine requires the sponsor to establish, through carefully controlled laboratory and clinical studies, as well as through other data, that the product is safe and effective for its approved indication(s) and use. FDA's multidisciplinary review teams then rigorously evaluate the sponsor's laboratory and clinical data, as well as other information, to help assess whether the safety, purity, and potency of a vaccine has been demonstrated.[10] Only when FDA's standards are met is a vaccine licensed.

FDA regulations explicitly state that "[a]pproval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products."[11] Therefore, the manufacturers of vaccines that have been licensed in the U.S. have necessarily demonstrated the safety of the vaccines within the meaning of the applicable statutory and regulatory provisions before the vaccines were licensed and allowed to be marketed.

For more information on FDA's thorough process for evaluating the safety of vaccines, see Appendix I of this letter, *Aspects of Vaccine Development and Process for Licensure*.

ii. Vaccine Safety Continues to Be Monitored Post-Licensure

FDA's oversight of vaccine safety continues after licensure of the product. Once the licensed vaccine is on the market, post-marketing surveillance of vaccine safety is conducted in order to detect any rare, serious, or unexpected adverse events, as well as to monitor vaccine lots. FDA employs multiple surveillance systems and databases to continue to evaluate the safety of these vaccines. In certain cases, FDA may require the manufacturer to conduct post-marketing studies to further assess known or potential serious risks.

b. An Emergency Use Authorization for a COVID-19 Preventative Vaccine Is Issued Only If the Relevant Statutory Standards Are Met

Congress established the Emergency Use Authorization (EUA) pathway to ensure that, during public health emergencies, potentially lifesaving medical products could be made available before being approved. The EUA process allows the Secretary of HHS, in appropriate circumstances, to declare that EUAs are justified for products to respond to certain types of

[8] 42 U.S.C. § 262(a)(2)(C)(i)(I).
[9] 21 CFR § 601.2(a).
[10] FDA, Vaccines, last updated January 2021, https://www.fda.gov/vaccines-blood-biologics/vaccines.
[11] 21 CFR § 601.2(d) (emphasis added).

threats. When such a declaration is made, FDA may issue an EUA, which is different from the regulatory process for vaccine licensure.

Section 564 of the Food Drug & Cosmetic Act (FD&C Act) (21 U.S.C. § 360bbb-3) authorizes FDA to, under certain circumstances, issue an EUA to allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by chemical, biological, radiological, or nuclear threat agents when there are no adequate, approved, and available alternatives.

On February 4, 2020, pursuant to section 564(b)(1)(C) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States (U.S.) citizens living abroad, and that involves the virus that causes COVID-19.[12] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564(b)(1) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)).[13]

Based on this declaration and determination, under section 564(c) of the FD&C Act (21 U.S.C. § 360bbb-3(c)), FDA may issue an EUA during the COVID-19 pandemic after FDA concludes that the following statutory requirements are met:

- The agent referred to in the March 27, 2020 EUA declaration by the Secretary (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.

- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.

- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

Although EUAs are governed under a different statutory framework than BLAs, FDA has made clear that issuance of an EUA for a COVID-19 vaccine would require that the vaccine demonstrated clear and compelling safety and efficacy in a large, well-designed Phase 3 clinical trial. In the guidance document *Emergency Use Authorization for Vaccines to Prevent COVID-19* (October 2020 Guidance), FDA has provided recommendations that describe key information

[12] HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[13] HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

that would support issuance of an EUA for a vaccine to prevent COVID-19.[14] In the October 2020 Guidance, FDA explained that, in the case of such investigational vaccines, any assessment regarding an EUA will be made on a case-by-case basis considering the target population, the characteristics of the product, the preclinical and human clinical study data on the product, and the totality of the available scientific evidence relevant to the product.[15] FDA has also stated, in this guidance, that for a COVID-19 vaccine for which there is adequate manufacturing information to ensure its quality and consistency, issuance of an EUA would require a determination by FDA that the vaccine's benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial that demonstrates the vaccine's safety and efficacy in a clear and compelling manner.[16]

A Phase 3 trial of a vaccine is generally a large clinical trial in which a large number of people are assigned to receive the investigational vaccine or a control. In general, in Phase 3 trials that are designed to show whether a vaccine is effective, neither people receiving the vaccine nor those assessing the outcome know who received the vaccine or the comparator.

In a Phase 3 study of a COVID-19 vaccine, the efficacy of the investigational vaccine to prevent disease will be assessed by comparing the number of cases of disease in each study group. For Phase 3 trials, FDA has recommended to manufacturers in guidance that the vaccine should be at least 50% more effective than the comparator, and that the outcome be reliable enough so that it is not likely to have happened by chance.[17] During the entire study, subjects will be monitored for safety events. If the evidence from the clinical trial meets the pre-specified criteria for success for efficacy and the safety profile is acceptable, the results from the trial can potentially be submitted to FDA in support of an EUA request.

Investigational COVID-19 vaccines continue to be studied in Phase 2 or Phase 3 trials. Following clinical trials, manufacturers analyze data prior to submitting to FDA a BLA to request approval from FDA to market the vaccine. A BLA for a new vaccine includes information and data regarding the safety, effectiveness, chemistry, manufacturing and controls, and other details regarding the product. During the current public health emergency, manufacturers may, with the requisite data and taking into consideration input from FDA, choose to submit a request for an EUA.

Importantly, FDA has made clear that any vaccine that meets FDA's standards for effectiveness is also expected to meet the Agency's safety standards. FDA has stated that the duration of safety follow-up for a vaccine authorized under an EUA may be shorter than with a BLA (which the Agency expects will ultimately be submitted by manufacturers of vaccines that are authorized under an EUA). Specifically, FDA's guidance to manufacturers recommends that data from Phase 3 studies to support an EUA include a median follow-up duration of at least 2 months after completion of the full vaccination regimen.[18] Furthermore, robust safety monitoring is conducted after a vaccine is made available. The monitoring systems include the

[14] Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry, October 2020 (October 2020 Guidance), https://www.fda.gov/media/142749/download.
[15] Id. at 3.
[16] Id. at 4.
[17] Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry, June 2020, https://www.fda.gov/media/139638/download.
[18] October 2020 Guidance at 10-11.

Vaccine Adverse Event Reporting System (VAERS), FDA's Biologics Effectiveness and Safety (BEST) System, and the Centers for Disease Control and Prevention's (CDC) Vaccine Safety Datalink. In addition, FDA has a partnership with the Centers for Medicare & Medicaid Services (CMS) to study vaccine safety. Other tools to monitor vaccine safety are under development. Collectively, these programs will help detect any new, unusual and rare side effects after vaccination that might not have been observed during clinical trials, as well as monitor for increases in any known side effects.

It is FDA's expectation that, following submission of an EUA request and issuance of an EUA, a sponsor would continue to evaluate the vaccine and would also work towards submission of a BLA as soon as possible.

III. Discussion

The Petition makes a request regarding clinical trials of COVID-19 vaccines that include or propose to include children. FDA's investigational new drug process applies to the development of new drugs and biological products, including vaccines.[19]

a. Investigational New Drugs

Before a vaccine is licensed (approved) by FDA for use by the public, FDA requires that it undergo a rigorous and extensive development program to determine the vaccine's safety and effectiveness. This development program encompasses preclinical research (laboratory research, animal studies[20]) and clinical studies. At the preclinical stage, the sponsor focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies. Clinical studies, in humans, are conducted under well-defined conditions and with careful safety monitoring through all the phases of the investigational new drug process. FDA's regulations governing the conduct of clinical investigations are set out at 21 CFR Part 312.

Before conducting a clinical investigation in the U.S. in which a new drug or biological product is administered to humans, a sponsor must submit an investigational new drug application (IND) to FDA.[21] The IND describes the proposed clinical study in detail and, among other things, helps protect the safety and rights of human subjects.[22] In addition to other information, an IND must contain information on clinical protocols and clinical investigators. Detailed protocols for proposed clinical studies permit FDA to assess whether the initial-phase trials will expose subjects to unnecessary risks. Information on the qualifications of clinical investigators (professionals, generally physicians, who oversee the administration of the experimental drug) permits FDA to assess whether they are qualified to fulfill their clinical trial duties. The IND

[19] See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).

[20] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[21] See 21 CFR § 312.20(a).

[22] For additional information regarding the IND review process and general responsibilities of sponsor-investigators related to clinical investigations see Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators; Draft Guidance for Industry, May 2015, https://www.fda.gov/media/92604/download.

includes commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB),[23] and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials, unless FDA informs the sponsor that the trial may begin earlier. During this time, FDA reviews the IND. FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and Phase 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.[24]

FDA's regulations provide that, once an IND is in effect, the sponsor may conduct a clinical investigation of the product, with the investigation generally being divided into three phases. With respect to vaccines, the initial human studies, referred to as Phase 1 studies, are generally safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase 2 studies may include up to several hundred individuals and are designed to provide information regarding the incidence of common short-term side effects such as redness and swelling at the injection site or fever and to further describe the immune response to the investigational vaccine. If an investigational new vaccine progresses past Phase 1 and Phase 2 studies, it may progress to Phase 3 studies. For Phase 3 studies, the sample size is often determined by the number of subjects required to establish the effectiveness of the new vaccine, which may be in the thousands or tens of thousands of subjects. Phase 3 studies provide the critical documentation of effectiveness and important additional safety data required for licensing.

Additionally, FDA regulations require that an IRB must review clinical investigations involving children as subjects covered by 21 CFR 50, subpart D and only approve those clinical investigations involving children as subjects that satisfy the criteria in 21 CFR 50, subpart D, Additional Safeguards for Children in Clinical Investigations. As explained in the preamble to the final rule, "[t]hese safeguards are intended to ensure that the rights and welfare of children who participate in clinical investigations are adequately protected."[25]

At any stage of development, if data raise significant concerns about either safety or effectiveness, FDA may request additional information or studies; FDA may also halt ongoing clinical studies. The FD&C Act provides a specific mechanism, called a "clinical hold," for prohibiting sponsors of clinical investigations from conducting the investigation (section

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[23] The IRB is a panel of scientists and non-scientists in hospitals and research institutions that oversees clinical research. IRBs approve clinical study protocols, which describe the type of people who may participate in the clinical study; the schedule of tests and procedures; the medications and dosages to be studied; the length of the study; the study's objectives; and other details. IRBs make sure that the study is acceptable, that participants have given consent and are fully informed of the risks, and that researchers take appropriate steps to protect patients from harm. See The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective web page, last updated November 2017, https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.

[24] 21 CFR § 312.22(a).

[25] Preamble to final rule, "Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products" (78 FR 12937 at 12938, February 26, 2013), https://www.federalregister.gov/documents/2013/02/26/2013-04387/additional-safeguards-for-children-in-clinical-investigations-of-food-and-drug.

505(i)(3) of the FD&C Act; 21 U.S.C. § 355(i)(3)), and FDA's IND regulations in 21 CFR § 312.42 identify the circumstances that may justify a clinical hold. Generally, a clinical hold is an order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or to suspend an ongoing investigation.[26]

b. The Citizen Petition

i. Petitioner's Request to Revoke all Emergency Use Authorizations for COVID-19 Vaccines and Refrain from Issuing any Future EUA or Approving any Future NDA, or BLA for any COVID-19 Vaccine for all Demographic Groups because the Current Risks of Serious Adverse Events or Deaths Outweigh the Benefits, and Because Existing, Approved Drugs Provide Highly Effective Prophylaxis and Treatment against COVID-19, Mooting the EUAs

Petitioner makes several requests regarding COVID-19 vaccines in the Petition and, in support of these requests, argues that (1) the rates of serious adverse events or deaths outweigh the benefits of these vaccines and (2) approved drugs provide highly effective prophylaxis/treatment against COVID, thereby "mooting" the EUAs. We interpret this as an argument that the authorizations of COVID-19 vaccines to date did not meet the relevant legal standard. Below, we address each of Petitioner's requests and the information provided by Petitioner in support of these requests.

1. Petitioner's Request to Revoke all Emergency Use Authorizations for COVID-19 Vaccines

In this section, we address Petitioner's request that FDA "revoke all EUAs . . . for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs." Petition at 1.

a. EUAs for COVID-19 Vaccines

As noted above in Section II above, FDA may issue an EUA during the COVID-19 public health emergency after FDA concludes that the statutory requirements provided in section 564 of the FD&C Act are met. In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates have been developed. COVID-19 vaccines that have been developed or are currently in development are based on various platforms and include mRNA, DNA, viral vectored, subunit, inactivated, and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain, as the immunogenic determinant.

To date, FDA has issued EUAs for three COVID-19 vaccines ("the Authorized COVID-19 Vaccines"), as described in the Scope of Authorization for these COVID-19 vaccines, pursuant

[26] 21 CFR § 312.42(a).

to section 564 of the FD&C Act. Additionally, FDA has expanded the authorized age range for one COVID-19 vaccine.

- On December 11, 2020, FDA issued an EUA for emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age and older.
    - On May 10, 2021, FDA authorized the emergency use of Pfizer-BioNTech COVID-19 Vaccine to include individuals 12 through 15 years of age.
- On December 18, 2020, FDA issued an EUA for emergency use of Moderna COVID-19 Vaccine for the prevention of COVID-19 in individuals 18 years of age and older.
- On February 27, 2021, FDA issued an EUA for emergency use of Janssen COVID-19 Vaccine for the prevention of COVID-19 in individuals 18 years of age and older.

The Agency issued these EUAs after a thorough evaluation of scientific data regarding the safety, effectiveness, and manufacturing information (which helps ensure product quality and consistency) of these COVID-19 vaccines and after reaching a determination that these vaccines meet the statutory requirements under section 564 of the FD&C Act. This letter incorporates by reference the EUA Review Memoranda for the Authorized COVID-19 Vaccines,[27] which discuss this determination, and the data upon which it was based, in detail as well as the Summary Basis of Regulatory Action for the BioNTech COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty).[28]

Petitioner argues that the authorizations for these vaccines should be revoked, and that future COVID vaccines should not be authorized or licensed, because (1) "the current risks of serious adverse events or deaths outweigh the benefits," and (2) "existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs." We address each of Petitioner's arguments, and data submitted in the Petition in support of these arguments, below.

FDA disagrees with Petitioner's position that the Authorized COVID-19 Vaccines did not meet the statutory standard at the time of authorization, and finds no basis in the information submitted in the Petition, or in any postmarket data regarding these vaccines, to support a revocation of any of these authorizations. FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. The

[27] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021) https://www.fda.gov/media/151613/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), https://www.fda.gov/media/144673/download; FDA, Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021) https://www.fda.gov/media/151611/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), https://www.fda.gov/media/146338/download.

[28] This letter incorporates by reference FDA's Summary Basis for Regulatory Action (SBRA) for the BioNTech BLA. This memorandum will be posted on www.fda.gov.

known and potential benefits of the Authorized COVID-19 Vaccines continue to outweigh their known and potential risks, given the risk of COVID-19 and related, potentially severe, complications. Furthermore**,** as explained below, there is no adequate, approved, and available alternative to the Authorized COVID-19 Vaccines for preventing COVID-19. Accordingly, this request is denied.

b. Standard for Revocation of EUAs is not Met for the Authorized COVID-19 Vaccines

Section 564(g)(2) of the FD&C Act provides the standard for revocation of an EUA. Under this statutory authority, FDA may revise or revoke an EUA if:

> (A) the circumstances described under [section 564(b)(1) of the FD&C Act] no longer exist;
> (B) the criteria under [section 564(c) of the FD&C Act] for issuance of such authorization are no longer met; or
> (C) other circumstances make such revision or revocation appropriate to protect the public health or safety.

FDA's guidance entitled *Emergency Use Authorization of Medical Products and Related Authorities* ("EUA Guidance"),[29] notes that once an EUA is issued for a product, in general, that EUA will remain in effect for the duration of the EUA declaration under which it was issued, "unless the EUA is revoked because the criteria for issuance . . . are no longer met or revocation is appropriate to protect public health or safety (section 564(f),(g) [of the FD&C Act])."[30] Regarding the circumstances that would make a revision or revocation appropriate to protect the public health or safety, FDA explains in the EUA guidance that

> Such circumstances may include significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.

[29] Emergency Use Authorization of Medical Products and Related Authorities; Guidance for Industry and Other Stakeholders, January 2017 (EUA Guidance), https://www.fda.gov/media/97321/download.
[30] Id. at 28.

EUA guidance at 29.

Thus, in addressing Petitioner's request for FDA to revoke the Authorized COVID-19 Vaccines, we assess whether any of the statutory conditions under which FDA may revoke an EUA are met, namely: (1) whether the circumstances justifying their issuance under section 564(b)(1) of the FD&C Act no longer exist, (2) whether the criteria for their issuance under section 564(c) of the FD&C Act are no longer met, and (3) whether other circumstances make a revision or revocation appropriate to protect the public health or safety.

i. Circumstances Continue to Justify the Issuance of the EUAs for the Authorized COVID-19 Vaccines

As explained above in section II.b., on February 4, 2020, pursuant to section 564(b)(1)(C) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves the virus that causes COVID-19.[31] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic ("COVID-19 EUA Declaration"), pursuant to section 564(b)(1) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)).[32]

Based on this declaration and determination, under section 564(c) of the FD&C Act (21 U.S.C. § 360bbb-3(c)), FDA may issue an EUA during the COVID-19 pandemic after FDA concludes that the statutory requirements provided in section 564(c) are met. Section 564(b)(2) sets forth the statutory standard for termination of an EUA declaration. An EUA declaration remains in place until the earlier of: (1) a determination by the HHS Secretary that the circumstances that precipitated the declaration have ceased (after consultation as appropriate with the Secretary of Defense) or (2) a change in the approval status of the product such that the authorized use(s) of the product are no longer unapproved. Neither of those statutory criteria is satisfied with respect to the Authorized COVID-19 Vaccines.

Thus, the circumstances described under section 564(b)(1) of the FD&C Act continue to exist. FDA therefore is not revoking the EUAs for the Authorized COVID-19 Vaccines under the authority in section 564(g)(2)(A) of the FD&C Act.

ii. The Criteria for The Issuance of the Authorized COVID-19 Vaccines Continue to Be Met

This section describes in detail why the criteria under section 564(c) of the FD&C Act continue to be met with respect to the Authorized COVID-19 Vaccines and why, therefore, FDA is not revoking the EUAs for the Authorized COVID-19 Vaccines under the authority in section 564(g)(2)(B) of the FD&C Act.

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[31] HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[32] HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

1. Serious or life-threatening disease or condition.

Section 564(c)(1) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "the agent(s) referred to in [the HHS Secretary's EUA declaration] can cause a serious or life-threatening disease or condition." FDA has concluded that SARS-CoV-2, which is the subject of the EUA declaration, meets this standard.

The SARS-CoV-2 pandemic continues to present an extraordinary challenge to global health and, as of August 3, 2021, has caused more than 199 million cases of COVID-19 and claimed the lives of more than 4.2 million people worldwide.[33] In the United States, more than 34 million cases and over 611,000 deaths have been reported to the CDC.[34] On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS, and the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020.
FDA is not aware of science indicating that there is any change in the ability of the SARS-CoV-2 virus to cause a serious or life-threatening disease or condition, namely COVID-19, nor has Petitioner provided any information about such a change. Therefore, the criterion under section 564(c)(1) continues to be met with respect to the Authorized COVID-19 Vaccines.

2. Evidence of Effectiveness

Section 564(c)(2)(A) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2."

FDA issued EUAs for the Authorized COVID-19 Vaccines after determining that, among other things, these products were demonstrated in clinical trials to prevent symptomatic and severe COVID-19 in vaccinated clinical trial subjects.[35] FDA is not aware of any data that changes this conclusion, nor has Petitioner provided any such data in the Petition. This section addresses Petitioner's arguments regarding the effectiveness of the Authorized COVID-19 vaccines and explains why the information submitted by Petitioner does not change FDA's analysis regarding the effectiveness of these vaccines.

After FDA approves a vaccine or authorizes a vaccine for emergency use, the vaccine continues to be studied to determine how well it works under real-world conditions. FDA, CDC, and other federal partners have been assessing, and will continue to assess, COVID-19 vaccine

[33] Johns Hopkins University School of Medicine, Coronavirus Resource Center, https://coronavirus.jhu.edu/map.html.
[34] CDC, COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases.
[35] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 23, https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 24, https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 25, https://www.fda.gov/media/146338/download.

effectiveness under real-world conditions. Such evaluations will help us understand if vaccines are performing as expected outside the more controlled setting of a clinical trial.

Petitioner raises concerns regarding the post-market effectiveness of the Authorized COVID-19 Vaccines (Petition at 6). Petitioner points to CDC-reported "breakthrough cases" to suggest that the Authorized COVID-19 Vaccines are not effective and argues that the EUAs for the Authorized COVID-19 Vaccines should therefore be revoked because the current risks of these vaccines outweigh their benefits. This perspective fails to recognize several important points regarding the concept of breakthrough cases and regarding the CDC publication cited in the Petition.

First, we note that the Letters of Authorization for the Authorized COVID-19 Vaccines require EUA-holders to report to VAERS "cases of COVID-19 that result in hospitalization or death, that are reported to [the EUA holder]."[36] Thus, the possibility that individuals who received one of the Authorized COVID-19 Vaccines could develop breakthrough COVID-19 cases was recognized by FDA when the Agency evaluated the EUA requests for these vaccines and determined that their known and potential benefits outweigh their known and potential and risks.

Second, the Authorized COVID-19 Vaccines are indicated to prevent *symptomatic* COVID-19,[37] not to prevent SARS-CoV-2 infection. Over 353 million doses of COVID-19 vaccines have been administered in the United States[38] and FDA's ongoing post authorization monitoring informs us that the known and potential benefits continue to outweigh the known and potential risks. Additionally, CDC's post-authorization data regarding the Authorized COVID-19 Vaccines continues to support FDA's conclusion that these vaccines prevent *symptomatic* COVID-19.[39]

Third, a vaccine does not need to be 100% effective in preventing the target disease in order to meet the licensure or EUA standard. It is expected that some vaccinated individuals will contract the target disease despite having been vaccinated against it. No FDA licensed or authorized vaccine is 100% effective, but scientific data has nevertheless demonstrated that vaccinations have been a very effective approach to protecting the public's health in the United States.[40]

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[36] Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Pfizer-BioNTech COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/144413/download; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Moderna COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/144637/download; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Janssen COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/146304/download.

[37] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 23, https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 24, https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 25, https://www.fda.gov/media/146338/download.

[38] CDC, COVID Data Tracker Weekly Review, Interpretive Summary for August 13, 2021, https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

[39] CDC, COVID-19 Vaccine Effectiveness Research, https://www.cdc.gov/vaccines/covid-19/effectiveness-research/protocols.html.

[40] Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.

Similarly, a COVID-19 vaccine need not be 100% effective in preventing symptomatic COVID-19, or even close to 100% effective in doing so, in order to have a significant effect in altering the course of the COVID-19 pandemic. As FDA noted in its June 2020 Guidance for Industry, Development and Licensure of Vaccines to Prevent COVID-19, ("The Vaccine Development and Licensure Guidance") "[t]o ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%."[41] This statistical consideration provided in the Vaccine Development and Licensure Guidance reflects FDA's assessment that a vaccine with at least 50 percent efficacy would have a significant impact on disease, both at the individual and societal level.

Finally, we note that Petitioner refers to "CDC-reported" breakthrough cases in support of its argument that there are effectiveness concerns with the Authorized COVID-19 Vaccines but fails to acknowledge that CDC reported a set of breakthrough cases that includes a large proportion of *asymptomatic* individuals who tested positive for SARS-CoV-2. Petitioner thus applies a narrower definition of the term "breakthrough case" to a set of cases than CDC has in its COVID-19 Vaccine Breakthrough Case Investigation.[42] Petitioner refers to breakthrough cases in which vaccinated individuals "fall ill and potentially transmit the virus" (Petition at 6) and states that "CDC reported over 9,000 'breakthrough cases' and 132 COVID-caused deaths among vaccinated people." Petition at 6.

CDC's objective in the COVID-19 Vaccine Breakthrough Case Investigation is to[43] ensure the COVID-19 vaccines are working as expected and to "identify patterns or trends" in:

- Patients' characteristics, such as age or underlying medical conditions
- The specific vaccine that patients received
- Whether a specific SARS-CoV-2 variant caused the infections"[44]

The objective of this investigation is not simply to count symptomatic COVID-19 cases. Currently, COVID-19 cases are increasing again in nearly all states. The highest rate of COVID-19 case spread is in areas with low vaccination rates.[45]

Petitioner's submitted data regarding CDC-reported "breakthrough cases" therefore does not present new data or information that the Agency has not previously considered regarding the effectiveness of the Authorized COVID-19 Vaccines. Available data regarding effectiveness of

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[41] Development and Licensure of Vaccines to Prevent COVID-19, Guidance for Industry, June 2020, at 14, https://www.fda.gov/media/139638/download.

[42] CDC, COVID-19 Vaccine Breakthrough Case Investigations and Reporting, https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html.

[43] CDC, COVID-19 Vaccine Breakthrough Case Investigations and Reporting, https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html.

[44] CDC, COVID-19 Vaccine Breakthrough Case Investigations and Reporting, https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html.

[45] "As of July 22 [2021], 35% of U.S. counties are experiencing high levels of community transmission. COVID-19 cases are on the rise in nearly 90% of U.S. jurisdictions, and we are seeing outbreaks in parts of the country that have low vaccination coverage." CDC, COVID Data Tracker Weekly Review, Interpretive Summary for July 23, 2021, available at https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html.

the Authorized COVID-19 Vaccines continues to support the conclusion that these vaccines may be effective in preventing COVID-19. FDA is not aware of any data that changes this conclusion, nor has Petitioner provided any such data in the Petition. Therefore, the criterion under section 564(c)(2)(A) continues to be met with respect to the Authorized COVID-19 Vaccines.

3. Benefit-Risk Analysis

Section 564(c)(2)(B) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "the known and potential benefits of the product, when used to diagnose, prevent, or treat [the identified serious or life-threatening disease or condition], outweigh the known and potential risks of the product . . . ." Petitioner argues that the current risks of serious adverse events or deaths associated with the Authorized COVID-19 Vaccines outweigh the benefits of COVID-19 vaccines. This section addresses Petitioner's arguments regarding the safety of COVID-19 vaccines and explains why the information submitted by Petitioner does not change FDA's analysis regarding the benefits and risks of the Authorized COVID-19 Vaccines.

FDA issued EUAs for the Authorized COVID-19 Vaccines after reaching a determination regarding each of these vaccines that, among other things, the known and potential benefits of the vaccine, when used to prevent COVID-19, outweigh its known and potential risks.[46] FDA is not aware of any data that changes this determination, nor has Petitioner provided any such data in the Petition. The known and potential benefits of the Authorized COVID-19 Vaccines, when used to prevent COVID-19, continue to outweigh their known and potential risks, given the risk of COVID-19 and related, potentially severe, complications.

Petitioner raises numerous concerns regarding safety of the Authorized COVID-19 Vaccines (Petition at 2-6) and asserts that the EUAs for the Authorized COVID-19 Vaccines should be revoked due in part to these safety concerns. For reasons explained below, FDA disagrees with Petitioner's assertions regarding the safety of the Authorized COVID-19 Vaccines.

As an initial matter, we note that the Petition discusses several assertions made by CDC and requests that have been directed to CDC. For requests intended for CDC, you should contact CDC directly.

a. Petitioner's Claims Regarding VAERS Data

[46] For an extensive discussion of FDA's analysis of the clinical trial data regarding the risks and benefits of each of the authorized COVID-19 Vaccines, *see* FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 49, https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 55, https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 59, https://www.fda.gov/media/146338/download. *See also*, FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), at 38, https://www.fda.gov/media/148542/download.

In arguing that the Authorized COVID-19 Vaccines should be revoked due, in part, to safety concerns, Petitioners assert that "Vaccine Adverse Event Reporting System (VAERS) data reveal unprecedented levels of deaths and other adverse events since the FDA issued Emergency Use Authorizations (EUAs) for three COVID vaccines. As of May 10, 2021, VAERS reported 4,434 deaths of people who received at least one COVID vaccination." As an initial matter, we note that VAERS is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed or authorized in the United States. VAERS is not designed to assess whether a reported adverse event was caused by a vaccine. This section explains vaccine safety surveillance, including VAERS, in greater detail below.

Regarding the number of VAERS reports submitted for the Authorized COVID-19 Vaccines, this figure can be attributed to multiple factors. First, we note that a large number of COVID-19 vaccine doses have been administered in the United States and that certain adverse event reporting by vaccination providers is *required* for the Authorized COVID-19 Vaccines. As of August 13, 2021, over 353,000,000 doses of the Authorized COVID-19 Vaccines have been administered.[47] We note that the crude number of VAERS reports of death is extremely small compared to the to the large number of people who have been vaccinated. The VAERS reporting rate for deaths (which is the number of VAERS death reports received out of the number of individuals vaccinated) for the Authorized COVID-19 Vaccines is actually very low (6,490 reports of death out of 346 million doses administered (0.0019%) as of August 2, 2021).[48] Petitioner's assertion fails to account for this fact.

For licensed vaccines, healthcare providers are legally required under 42 USC 300aa-25 to report to VAERS two categories of adverse events: "[a]ny adverse event listed in the VAERS Table of Reportable Events Following Vaccination that occurs *within the specified time period after vaccination* [and] [a]n adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine"[49] Vaccine manufacturers are also required to report to VAERS all adverse events that come to their attention.[50]
Under the EUAs for the Authorized COVID-19 Vaccines, however, vaccination providers are required to report to VAERS serious adverse events following vaccination with the Authorized COVID-19 Vaccines, "irrespective of attribution to vaccination" and without a specified time period after vaccination.[51] Another contributing factor is the v-safe system,[52] which is a new CDC smartphone-based active-surveillance system in which participants who have been

[47] CDC, COVID Data Tracker, COVID-19 Vaccinations in the United States, https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total.
[48] CDC, Selected Adverse Events Reported after COVID-19 Vaccination, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.
[49] VAERS, Frequently Asked Questions, https://vaers.hhs.gov/faq.html (emphasis added).
[50] 21 CFR 600.80. See also VAERS, Frequently Asked Questions, https://vaers.hhs.gov/faq.html.
[51] Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Pfizer-BioNTech COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/144413/download; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Moderna COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/144637/download; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Janssen COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, https://www.fda.gov/media/146304/download.
[52] CDC, v-safe Overview, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html.

vaccinated may voluntarily enroll. This system was developed for the COVID-19 vaccination program. V-safe sends text messages and web surveys to participants who can report side effects following receipt of a COVID-19 vaccine. If a participant indicates through the v-safe surveys that he or she required medical care at any time, CDC calls the participant to complete a report through VAERS. This system is unique to COVID-19 vaccines and may be contributing to the number of VAERS reports submitted for the Authorized COVID-19 Vaccines.
Finally, another potential factor is the concept of "stimulated reporting."[53] Because of extensive media coverage and awareness of the public health emergency – and of the Authorized COVID-19 Vaccines and their reported side effects –vaccine recipients, health care providers, and others are more likely to report adverse events for the Authorized COVID-19 Vaccines than for other vaccines that have been widely available for longer periods of time. Additionally, one of the articles submitted by Petitioner in support of their argument actually provides support for this explanation for the number of VAERS reports submitted for the Authorized COVID-19 Vaccines. The article notes "[t]he relatively rapid increase in numbers of reports to VAERS following the introduction and initial uptake of a new vaccine, an expected occurrence, has been *misinterpreted as actual increases in incidence of adverse events and vaccine related risk*."[54] Petitioner's argument regarding VAERS data for the Authorized COVID-19 Vaccines is unavailing because it fails to account for the factors outlined above.

In addressing Petitioner's assertion regarding VAERS claims, this section addresses the extensive vaccine safety surveillance efforts, in addition to VAERS, that are in place for the Authorized COVID-19 Vaccines.[55] FDA is monitoring the safety of the Authorized COVID-19 Vaccines through both passive and active safety surveillance systems. FDA is doing so in collaboration with the Centers for Disease Control and Prevention (CDC), the Centers for Medicare and Medicaid Services (CMS), the Department of Veterans Affairs (VA), and other academic and large non-government healthcare data systems.

In addition, FDA participates actively in ongoing international pharmacovigilance efforts, including those organized by the International Coalition of Medicines Regulatory Authorities

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[53] We note that an article submitted by Petitioner in support of their arguments regarding VAERS acknowledges this concept: "Like all spontaneous public health reporting systems, VAERS has limitations. VAERS is subject to reporting bias, including underreporting of adverse events – especially common, mild ones– and stimulated reporting, which is elevated reporting that might occur in response to intense media attention and increased public awareness, such as during the 2009 H1N1 pandemic influenza vaccination program" Shimabukuro et al., Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), Vaccine (Nov. 4, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/. See also "The number of reports and reporting rate following 2009-H1N1 vaccination were higher than following 2009–2010 seasonal influenza vaccines for all age groups. These findings, however, should be interpreted in light of the publicity around the 2009-H1N1 vaccine and efforts to increase reporting to VAERS. Heightened public awareness and stimulated reporting likely enhanced reporting to VAERS. Furthermore, although 2009-H1N1 was licensed similarly to seasonal influenza vaccines, it was likely perceived as a 'new' vaccine by the public and susceptible to the known tendency (i.e., the Weber effect) for adverse events to be reported more frequently following newly licensed products." Vellozzi, et al., Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009–January 31, 2010, Vaccine (Oct. 21, 2010), https://www.sciencedirect.com/science/article/pii/S0264410X10013319.

[54] Shimabukuro et al., Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), Vaccine (Nov. 4, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/ (emphasis added).

[55] FDA, COVID-19 Vaccine Safety Surveillance, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance.

(ICMRA) and the World Health Organization (WHO). These efforts are in addition to the pharmacovigilance efforts being undertaken by the individual manufacturers for authorized vaccines. A coordinated and overlapping approach using state-of the art technologies has been implemented. As part of our efforts to be transparent about our COVID-19 vaccine safety monitoring activities, FDA is posting summaries of the key safety monitoring findings on the FDA website. [56]

i. Vaccine Safety Surveillance

Passive Surveillance

VAERS is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed or authorized in the United States. Passive surveillance is defined as unsolicited reports of adverse events that are sent to a central database or health authority. In the United States, these are received and entered into VAERS, which is co-managed by FDA and CDC. In the current pandemic, these reports are being used to monitor the occurrence of both known and unknown adverse events, as providers of COVID-19 vaccines are required to report serious adverse events to VAERS.
As part of FDA and CDC's multi-system approach to post-licensure and post-authorization vaccine safety monitoring, VAERS is designed to rapidly detect unusual or unexpected patterns of adverse events, also known as "safety signals." VAERS reports generally cannot be used to determine if a vaccine caused or contributed to an adverse event or illness. If the VAERS data suggest a possible link between an adverse event and vaccination, the relationship may be further studied in a controlled fashion.[57]

Anyone can make a report to VAERS, including vaccine manufacturers, private practitioners, state and local public health clinics, vaccine recipients, and their parents or caregivers. Surveillance programs like VAERS perform a critical function by generating signals of potential problems that may warrant further investigation.

VAERS is not designed to assess causality. It is often difficult to determine with certainty if a vaccine caused an adverse event reported to VAERS. Many events that occur after vaccination can happen by chance alone. Some adverse events are so rare that their association with a vaccine is difficult to evaluate. In addition, we often receive reports where there is no clear clinical diagnosis. FDA draws upon multiple sources of data and medical and scientific expertise to assess the potential strength of association between a vaccine, including COVID-19 vaccines, and a possible adverse event.

If VAERS monitoring suggests that a vaccine might be causing a health problem, additional scientifically rigorous studies or investigations can be performed by FDA and CDC. Monitoring and analysis of VAERS reports typically includes daily in-depth medical review of all serious reports, statistical data mining techniques, and epidemiological analysis. We look for patterns and similarities in the onset timing and clinical description. We review published literature to

[56] FDA, COVID-19 Vaccine Safety Surveillance, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance
[57] FDA, VAERS Overview, https://www.fda.gov/vaccines-blood-biologics/vaccine-adverse-events/vaers-overview.

understand possible biologic hypotheses that could plausibly link the reported adverse event to the vaccine. We review the pre-licensure or pre-authorization data and any other post-marketing studies that have been conducted. We also consider "background rate," meaning the rate at which a type of adverse event occurs in the unvaccinated general population. When necessary, we discuss the potential adverse event with our federal and international safety surveillance partners. We also carefully evaluate unusual or unexpected reports, as well as reports of "positive re-challenges" (adverse events that occur in the same patient after each dose received). When there is sufficient evidence for a potential safety concern, we may proceed to conduct large studies, and we may coordinate with our federal, academic, and private partners to further assess the potential risk after vaccination. In addition, when potential safety issues arise, they are often presented to various U.S. government advisory committees, including the Vaccines and Related Biological Products Advisory Committee, the Advisory Committee on Immunization Practices (ACIP), and the Advisory Committee on Childhood Vaccines, and are often discussed with experts from other countries and from the World Health Organization. Federal agencies that assist in population-based vaccines safety studies include the CDC, Centers for Medicaid and Medicare (CMS), the Department of Defense (DoD), and the Indian Health Services (IHS). In addition, we generally communicate and work with international regulatory authorities and international partners to conduct studies in vaccine safety.

Active Surveillance

Active surveillance involves proactively obtaining and rapidly analyzing information related to millions of individuals and recorded in large healthcare data systems to verify safety signals identified through passive surveillance or to detect additional safety signals that may not have been reported as adverse events to passive surveillance systems. FDA is conducting active surveillance using the Sentinel BEST (Biologics Effectiveness and Safety) System and the CMS system, and is also collaborating with other federal and non-federal partners.

BEST

To elaborate further, the BEST system,[58] which is part of the Sentinel initiative,[59] comprises large-scale claims data, electronic health records (EHR), and linked claims-EHR databases with a data lag of approximately three months. The system makes use of multiple data sources and enables rapid queries to detect or evaluate adverse events as well as studies to answer specific safety questions for vaccines. The linked claims-EHR database makes it possible to study the safety of vaccines in sub-populations with pre-existing conditions or in pregnant women. The major partners for BEST currently are Acumen, IBM Federal HealthCare, IQVIA, and Columbia University and many affiliated partners such as MedStar Health, BlueCross BlueShield of

[58] CBER Biologics Effectiveness and Safety (BEST) System, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system.
[59] FDA's Sentinel Initiative, https://www.fda.gov/safety/fdas-sentinel-initiative.

America, the Observational Health Data Sciences and Informatics (OHDSI), OneFlorida, University of California and several others.[60]

Using BEST, CBER plans to monitor about 15 adverse events[61] that have been seen with the deployment of previous vaccines but have yet to be associated with a safety concern for an authorized COVID-19 vaccine at this time. CBER further plans to use the BEST system to conduct more in-depth analyses should a safety concern be identified from sources such as VAERS.

CMS

FDA has worked over the past several years with CMS to develop capabilities for routine and time-sensitive assessments of the safety of vaccines for people 65 years of age and older using the Medicare Claims database.[62] Because it was already in place, this system was immediately put into use for COVID-19 vaccine surveillance to monitor for adverse events.[63]

During the current pandemic, FDA, CMS, and CDC have already used the Medicare data to publish a study showing that frailty, comorbidities, and race/ethnicity were strong risk factors of COVID-19 hospitalization and death among the U.S. elderly.[64]

VSD

In addition, the Vaccine Safety Datalink (VSD) is a collaborative project between CDC's Immunization Safety Office and nine health care organizations. As noted on the CDC's

[60] To confirm the utility of the BEST system for situations such as COVID-19 vaccine surveillance, a test case was conducted. This study aimed to replicate a previous study by the CDC's Vaccine Safety Datalink (VSD) (Klein et al. Pediatrics 2010) that examined the databases and analytic capabilities of the new system. The objective of this study was to test the new system's ability to reproduce the increased risk of febrile seizures in children receiving the first dose of measles-mumps-rubella-varicella (MMRV) vaccine, compared to that of MMR and varicella vaccines separately but on the same day. The results of the study met the objectives and demonstrated the ability of the BEST Initiative data network to run a complex study protocol at multiple sites using a distributed data network and the Observational Medical Outcomes Partnership Common Data Model (organizing disparate data sources into the same database design using a common format).

[61] Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring, Draft Protocol (December 31, 2020), https://www.bestinitiative.org/wp-content/uploads/2021/01/C19-Vaccine-Safety-AESI-Background-Rate-Protocol-2020.pdf.

[62] CMS, Standard Analytical Files (Medicare Claims) – LDS, https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/StandardAnalyticalFiles.

[63] As one example of the capabilities of this system, FDA, CMS, and CDC evaluated the risk of Guillain-Barré syndrome (GBS) following influenza vaccination after CDC's Vaccine Safety Datalink, identified safety signals suggesting an increased risk of GBS following high-dose influenza vaccinations and Shingrix vaccinations during the 2018-2019 influenza season. CBER, CDC, and CMS formed working groups in February 2019 to refine these safety signals in the CMS data.

[64] Hector S Izurieta, David J Graham, Yixin Jiao, Mao Hu, Yun Lu, Yue Wu, Yoganand Chillarige, Michael Wernecke, Mikhail Menis, Douglas Pratt, Jeffrey Kelman, Richard Forshee, Natural History of Coronavirus Disease 2019: Risk Factors for Hospitalizations and Deaths Among >26 Million US Medicare Beneficiaries, The Journal of Infectious Diseases, Volume 223, Issue 6, 15 March 2021, Pages 945–956, https://doi.org/10.1093/infdis/jiaa767 https://academic.oup.com/jid/article/223/6/945/6039057.

webpage, the VSD started in 1990 and continues today in order to monitor safety of vaccines and conduct studies about rare and serious adverse events following immunization.

The VSD uses electronic health data from each participating site. This includes information on vaccines: the kind of vaccine given to each patient, date of vaccination, and other vaccinations given on the same day. The VSD also uses information on medical illnesses that have been diagnosed at doctors' offices, urgent care visits, emergency department visits, and hospital stays. The VSD conducts vaccine safety studies based on questions or concerns raised from the medical literature and reports to the Vaccine Adverse Event Reporting System (VAERS). When there are new vaccines that have been recommended for use in the United States or if there are changes in how a vaccine is recommended, the VSD will monitor the safety of these vaccines.

The VSD has a long history of monitoring and evaluating the safety of vaccines. Since 1990, investigators from the VSD have published many studies to address vaccine safety concerns.[65]

In summary, in collaboration and coordination with several different partners, FDA has assembled passive surveillance systems - including VAERS - and active surveillance systems that can detect and refine safety findings with the Authorized COVID-19 Vaccines in a relatively rapid manner. These systems can also potentially be leveraged to assess safety in specific subpopulations and to assess vaccine effectiveness.

ii. Articles Submitted in Petition Regarding Vaccine Surveillance

We note at the outset that Petitioner raises concerns regarding the methodology by which CDC calculated rates of anaphylactic adverse events post-vaccination. Such concerns are best directed to CDC and are outside the scope of FDA's Petition response.

Regarding Petitioner's contention that a low percentage of adverse events have been reported to VAERS and that therefore "the safety of COVID vaccines is considerably worse than it currently appears" (Petition at 4), as explained in detail above in this section, VAERS is only one part of a multi-tiered vaccine safety surveillance system, so the information derived from VAERS reports does not represent the full extent of vaccine safety information being monitored by FDA and its federal partners.

Specifically, Petitioner cites to three studies in support of the argument that "[g]iven that only 1 to 13% of adverse reactions have been reported to the FDA and CDC via the VAERS passive reporting system, according to Lazarus et al., the high number of adverse events and deaths following COVID vaccines is alarming." Petition at 5. The articles cited by Petitioner in support of this contention do not support Petitioner's position that, due to underreporting of adverse events, the rate of reported adverse events associated with COVID-19 vaccination is low in comparison to the actual rate of adverse events. As discussed above in this section, there are several factors unique to the surveillance of the Authorized COVID-19 Vaccines that have

[65] *See, e.g.*, CDC, White Paper on the Safety of the Childhood Immunization Schedule, Vaccine Safety Datalink, available at https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf.

contributed to the number of VAERS reports submitted for these vaccines. Petitioner's argument that adverse events associated with the Authorized COVID-19 Vaccines are underreported because of the figures presented in the articles cited fail to account for any of those factors that are unique to the Authorized COVID-19 Vaccines.

Petitioner cites to a publication from the Agency for Healthcare Research and Quality (Lazarus et al.) in support of the argument that deaths and adverse events associated with the Authorized COVID-19 Vaccines are underreported because "only 1 to 13% of adverse reactions have been reported to the FDA and CDC via the VAERS passive reporting system" (Petition at 5), and therefore the actual rate of COVID-19 Vaccine adverse events is significantly higher than reported.[66] As an initial matter, we note that the language cited from the Lazarus article is referring to adverse event reporting for drugs and vaccines, not just vaccine adverse events reported to VAERS.[67] Furthermore, as explained in detail above, several factors have contributed to the number of VAERS reports submitted for the Authorized COVID-19 Vaccines. The issues raised in this article regarding underreporting of drug adverse event reporting are not directly relevant to the claims Petitioner makes regarding adverse event reporting for the Authorized COVID-19 Vaccines. The article was published in 2010 and does not consider the numerous factors outlined above regarding reporting of adverse events following COVID-19 vaccination.

Petitioner cites to a journal article in the publication *Vaccine*[68] regarding VAERS safety monitoring in support of their argument that adverse event reports for the Authorized COVID-19 Vaccines are underreported. This article generally discusses the limitations of VAERS and passive surveillance, which are well-understood by the FDA and which are discussed in this letter. Additionally, this article notes "[p]erhaps the two most common misconceptions about VAERS are that temporally associated reports represent true adverse reactions caused by vaccination, and that VAERS reports equate to rates of adverse events or indicate risk of adverse events associated with vaccination."[69] This statement from the article demonstrates the flaws underlying Petitioner's claims that the Authorized COVID-19 Vaccines are unsafe due to the number of serious adverse events reported to VAERS following administration of these vaccines. Additionally, the article notes "[t]he relatively rapid increase in numbers of reports to VAERS following the introduction and initial uptake of a new vaccine, an expected occurrence, has been misinterpreted as actual increases in incidence of adverse events and vaccine related risk."[70] Thus, the article cited by Petitioner directly contradicts Petitioner's claims regarding the safety of the Authorized COVID-19 Vaccines based on the number of VAERS adverse event reports associated with these vaccines.

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[66] Lazarus et al., Electronic Support for Public Health-Vaccine Adverse Event Reporting System, Agency for Healthcare Research and Quality, HHS (Sept. 30, 2010), https://digital.ahrq.gov/ahrq-funded-projects/electronic-support-public-health-vaccine-adverse-event-reporting-system.
[67] Id. at 6.
[68] Shimabukuro et al., Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), Vaccine (Nov. 4, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/.
[69] Id. at 9.
[70] Id.

Finally, Petitioner also cites to a journal article in the American Journal of Public Health.[71] This article does not raise issues that have not already been addressed in this letter's discussion of safety surveillance. For instance, the article notes that passive surveillance has several limitations, specifically, passive surveillance may involve underreporting of adverse events, and passive surveillance data is not adequate to determine causation. Additionally, this article notes that passive surveillance can provide valuable information, "[n]evertheless, if reporting is reasonably consistent, it may be possible to detect changes in trends of known common adverse events."[72]

Therefore, the articles submitted by Petitioner do not present data or information regarding the Authorized COVID-19 Vaccines that change the Agency's analysis regarding the benefits and risks of the Authorized COVID-19 Vaccines.

Petitioner further asserts that extensive safety information regarding vaccines is inaccessible to the public ("the VAERS database is the only safety database to which the public has access. The government withholds extensive safety information from the public despite having at least ten additional data sources and expert consultants to analyze these data . . . ." Petition at 2.). This contention represents a misunderstanding by Petitioner of the sources of data analyzed by FDA and its federal partners, and of the types of information available to the public.
As noted above, Petitioner's questions regarding databases operated by other federal partners, such as DOD, CMS, CDC, VA, should be directed to those federal entities. Regarding FDA's BEST system, Petitioner erroneously claims that the public does not have access to the information on this system. As noted above, the BEST system,[73] which is part of the Sentinel initiative,[74] comprises large-scale claims data, electronic health records (EHR), and linked claims-EHR databases with a data lag of approximately three months. The system makes use of multiple data sources and enables rapid queries to detect or evaluate adverse events as well as studies to answer specific safety questions for vaccines. The system is not intended to be a source of raw EHR data. Instead, as explained on FDA's webpage describing the BEST system, the purpose of the BEST system is to: (1) build data, analytics, infrastructure for an active, large-scale, efficient surveillance system for biologic products; and (2) develop innovative methods to utilize electronic health records (EHR) effectively and establish automated adverse events reporting, utilizing natural language processing and artificial intelligence.[75] BEST does not have access to the raw, identifiable data. BEST data partners analyze the raw data per publicly posted protocols and send the results in aggregated form to BEST for review. The information is summarized in either final reports, manuscripts or public presentations. BEST publicly posts study protocols of surveillance activities on the BEST site with open public comments regarding the protocols, final reports and manuscripts as well as communication on CBER safety site and public meetings, e.g., VRBPAC, where appropriate. These protocols delineate the scientific approach to analyzing the raw data, where in the raw form is of limited utility to the public, to

[71] S. Rosenthal and R. Chen, The reporting sensitivities of two passive surveillance systems for vaccine adverse events, American Journal of Public Health (Dec. 1995), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1615747/.
[72] Id.
[73] CBER Biologics Effectiveness and Safety (BEST) System, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system.
[74] FDA's Sentinel Initiative, https://www.fda.gov/safety/fdas-sentinel-initiative.
[75] CBER Biologics Effectiveness and Safety (BEST) System, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system.

generate information on vaccine safety. The final reports and manuscripts summarize the information and conclusions inferred from well-conducted surveillance studies.

iii. FDA Has Responded to Safety Signals Related to the Authorized COVID-19 Vaccines by Extensively Reviewing Data, Updating the Authorized Labeling, and Communicating to the Public

Petitioner further asserts that "FDA and CDC have not responded to these data by issuing any warnings or restricting the use of these vaccines." Petition at 2. This assertion is inaccurate. As explained in detail above, FDA and its federal partners, including CDC, have closely monitored post-market safety data regarding the Authorized COVID-19 Vaccines. FDA has worked to identify and investigate serious adverse events occurring in people after receiving the Authorized COVID-19 Vaccines, and to communicate these risks to the public and revise the authorized labeling to reflect these risks in a timely fashion.[76] The surveillance systems that are in place to monitor the safety of COVID-19 vaccines authorized for emergency use are working, as demonstrated by FDA's and CDC's work to identify and investigate these serious adverse events in a timely manner.

Adverse events reported to VAERS following administration of one of the authorized COVID-19 vaccines are reviewed to assess possible safety concerns. Such review of VAERS data regarding the authorized COVID-19 vaccines has been conducted since these vaccines were authorized. Such review has prompted the Agency to take action with respect to the currently authorized COVID-19 vaccines:

- On April 13, 2021, FDA and CDC recommended a pause in the use of the Janssen COVID-19 vaccine following six VAERS reports in the U.S. of thrombosis with thrombocytopenia.[77] The FDA and CDC thoroughly reviewed VAERS and other post-authorization information and data related to the Janssen COVID-19 vaccine during the recommended pause. This review included two meetings of ACIP. Following a thorough safety review, FDA determined that the available data show that the Janssen COVID-19 vaccine's known and potential benefits outweigh its known and potential

[76] Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Sections 5.2 and 5.3 Warnings and Precautions Regarding Thrombosis with Thrombocytopenia and GBS, https://www.fda.gov/media/146304/download; Pfizer-BioNTech COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, https://www.fda.gov/media/144413/download; Moderna COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, https://www.fda.gov/media/144637/download.

[77] We note that Petitioner mentions that Denmark, among other nations, has "banned" the Janssen COVID-19 vaccine. To the extent Petitioner relies on this ban as support for Petitioner's request that FDA revoke the EUA for this vaccine, we note that Denmark and other nations' actions with respect to the use of this vaccine are outside purview of FDA's work, so we cannot comment on decisions they make under their public health regulatory framework.

risks in individuals 18 years of age and older. As a result of this review, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was updated to include a Warning pertaining to the risk of thrombosis with thrombocytopenia. The Fact Sheet for Recipients and Caregivers was also updated to include information about these serious adverse events. The FDA and CDC conducted extensive outreach to providers and clinicians to ensure they were made aware of the potential for these adverse events and could properly recognize and manage thrombosis with thrombocytopenia in individuals who receive the Janssen COVID-19 Vaccine.

- On June 25, 2021, following review of VAERS reports, FDA required revisions to the authorized labeling for the Pfizer-BioNTech COVID-19 vaccine and the Moderna COVID-19 vaccine to add a warning regarding the suggested increased risks of myocarditis and pericarditis. This update to the authorized labeling for these vaccines followed an extensive review of information and the discussion by CDC's ACIP meeting on June 23, 2021. As of July 26, 2021, the FDA and the Centers for Disease Control and Prevention (CDC) have received 1,194 reports of myocarditis or pericarditis occurring among people ages 30 and younger who received either Moderna or Pfizer-BioNTech COVID-19 vaccines, particularly following the second dose.[78] Through follow-up, including medical record reviews, the FDA and CDC had confirmed 699 cases of myocarditis or pericarditis.[79]
- On July 13, 2021, FDA required revisions to the vaccine recipient and vaccination provider fact sheets for the Janssen COVID-19 Vaccine to include information pertaining to a suggested increased risk of Guillain-Barré Syndrome (GBS) during the 42 days following vaccination. Based on an analysis of Vaccine Adverse Event Reporting (VAERS) data, at that time, there had been 100 reports of presumptive GBS following vaccination with the Janssen vaccine after approximately 12.5 million doses administered. Of these reports, 95 of them were serious and required hospitalization. There was one reported death. As noted in the Janssen Fact Sheet for Healthcare Providers Administering Vaccine, because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Each year in the United States, an estimated 3,000 to 6,000 people develop GBS. Most people fully recover from the disorder. FDA publicly presented this issue, and information regarding these 100 reports of presumptive GBS, to the ACIP on July 22, 2021.[80]

During each of these post-authorization reviews and labeling changes, the FDA has evaluated the available post-authorization information for the authorized COVID-19 Vaccines and continues to find the known and potential benefits clearly outweigh the known and potential risks.

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[78] CDC, COVID-19 Reported Adverse Events, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.
[79] Id.
[80] FDA, CDC ACIP Meeting Presentation, Guillain-Barré Syndrome (GBS) after Janssen COVID-19 Vaccine: Vaccine Adverse Event Reporting System (VAERS), July 22, 2021, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/02-COVID-Alimchandani-508.pdf.

iv. Petitioner's Claims Regarding Anaphylaxis

Petitioner cites to a study of acute allergic reactions to mRNA COVID-19 vaccines in support of their argument that adverse event rates for COVID-19 vaccines have been miscalculated by CDC.[81] As stated above, questions relating to CDC are best directed to that Agency. We note, however, that this journal article states, immediately after the sentence quoted by Petitioner, "[h]owever, the overall risk of anaphylaxis to an mRNA COVID-19 vaccine remains extremely low and largely comparable to other common health care exposures. Although cases were clinically compatible with anaphylaxis, the mechanism of these reactions is unknown." The paper further states, in describing the limitations of the study, that "[a] northeastern US cohort may not be generalizable." Thus, Petitioner is inappropriately generalizing the results of this study in an attempt to compare the results to the CDC's reported data and conclude that the safety of COVID vaccines is "considerably worse than it currently appears." Petition at 4.

Additionally, we note that the authorized labeling for all the Authorized COVID-19 vaccines already contain warnings regarding the risk of anaphylaxis as a potential adverse event. Thus, the risk of anaphylaxis is a potential safety issue FDA is already aware of, and Petitioner's argument, and the article submitted in support of this argument, does not change FDA's conclusions regarding the safety of the Authorized COVID-19 vaccines.

v. Animal Toxicology and Pharmacokinetic Studies of COVID-19 Vaccines

Petitioner raises concerns regarding FDA's vaccine safety assessment. Specifically, Petitioner states that other "problems with vaccine safety assessment *may exist* because of inadequate animal toxicology and pharmacokinetic studies of COVID vaccines." Petition at 5; emphasis added. As an initial matter, we note that Petitioner's concerns regarding the vaccine safety assessment for COVID-19 vaccines involves speculation regarding whether problems actually exist ("problems with vaccine safety assessment *may exist* . . ."), and Petitioner fails to point to any specific problems that result or may result from the allegedly inadequate studies. Regarding Petitioner's claims, in general, when evaluating the safety data regarding a vaccine, FDA considers data from animal studies (if such pre-clinical studies were performed) as one part of the full body of evidence regarding the vaccine. In addition to data from animal studies, if available, FDA evaluates data from in vitro studies and conducts a safety assessment of data from clinical studies.

Thus, although Petitioner raises several concerns and cites to several articles regarding risks of COVID-19 vaccination, FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. Therefore, the

[81] Blumenthal KG, Robinson LB, Camargo CA, et al., Acute Allergic Reactions to mRNA COVID-19 Vaccines, JAMA. 2021;325(15):1562–1565. doi:10.1001/jama.2021.3976, https://jamanetwork.com/journals/jama/fullarticle/2777417.

criterion under section 564(c)(2)(B) continues to be met with respect to the Authorized COVID-19 Vaccines.

4. No Alternatives

As noted above, Petitioner requests that "FDA should revoke all EUAs and refrain from approving any future EUA . . . for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs." Petition at 1. Section 564(c)(3) of the FD&C Act provides one of the required statutory factors that must be met in order for a product to be granted an EUA. This statutory provision requires that "there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating [the serious or life-threatening disease or condition]."[82] To the extent Petitioner's contention can be interpreted as an argument that there are adequate, approved, available drugs indicated for the prevention of COVID-19 (and that therefore the requirement in section 564(c)(3) of the FD&C Act that there is no "adequate, approved, and available alternative to the Authorized COVID-19 Vaccines for preventing COVID-19 is not met), this argument is erroneous.

As explained in the Decision Review Memoranda for the Authorized COVID-19 Vaccines, at the time each COVID-19 vaccine EUA was issued, there were no FDA-approved drugs or biological products indicated to prevent COVID-19 in any population because no vaccine or other medical product was the subject of an approved marketing application for prevention of COVID-19.[83] This is still true today, with the exception of the BLA for BioNTech's COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty), which is now approved for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The EUA for Pfizer-BioNTech COVID-19 Vaccine remains in effect. This EUA will continue to cover individuals 12 through 15 years of age, to cover the administration of a third dose to certain immunocompromised individuals 12 years of age and older, and to cover individuals 16 years of age and older until sufficient approved vaccine can be manufactured and distributed. Similarly, the EUA for the Moderna COVID-19 Vaccine and the Janssen COVID-19 Vaccine remain in effect for individuals 18 years of age and older. Although FDA has approved one new drug application (NDA) for remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization, this drug is not for prevention of COVID-19. Several other therapies are currently available under EUA, but not FDA approved, for treatment of COVID-19, and one is available under EUA, but not FDA approved, for post-exposure prophylaxis in a limited population. These products that are available under EUA are not considered "approved" products for purposes of section

[82] The term "approved," for purposes of section 564(c) of the FD&C Act, means a product is approved, licensed, or cleared by FDA under section 505, 510(k), or 515 of the FD&C Act or section 351 of the PHS Act, as applicable, and this term is indication-specific. *See*, section 564(a)(2) of the FD&C Act. *See also*, EUA guidance at 3.
[83] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 8-9, https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 9, https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 9, https://www.fda.gov/media/146338/download.

564(c)(3) because they are not the subject of an approved marketing application (i.e., they are not approved under an NDA or BLA).

Thus, Petitioner's assertion that the EUAs for the Authorized COVID-19 Vaccines are "mooted" by the existence of drugs approved to prevent COVID-19 is incorrect.

5. No Other Circumstances Make A Revision or Revocation Appropriate to Protect the Public Health or Safety

As noted above, section 564(g)(2)(C) of the FD&C Act provides that FDA may revise or revoke an EUA if circumstances justifying its issuance (under section 564(b)(1)) no longer exist, the criteria for its issuance are no longer met, or other circumstances make a revision or revocation appropriate to protect the public health or safety. The EUA guidance explains that such other circumstances may include:

> significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.[84]

As of the date of this writing, FDA has not identified any such circumstances that would make revocation of any of the Authorized COVID-19 Vaccines appropriate to protect the public health or safety. As stated previously in this response, FDA determined the EUA standard is met for the three authorized COVID-19 vaccines because data submitted by the sponsors demonstrated in a clear and compelling manner that the known and potential benefits of these products, when used to prevent COVID-19, outweigh the known and potential risks of these products, and that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating COVID-19.

As described in detail in section III.b.i.1.b above, FDA has identified circumstances that have made revision of the EUAs for the Authorized COVID-19 Vaccines appropriate, and,

[84] EUA Guidance at 29.

accordingly, has required changes to the authorized labeling for the Authorized COVID-19 Vaccines.[85]

Additionally, as explained above, FDA finds no basis in the information submitted in the Petition, or in any postmarket data regarding the Authorized COVID-19 Vaccines, to support a revocation of any of these EUAs, nor has Petitioner provided any such information in the Petition. FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. Furthermore, there are no other circumstances that make a revision or revocation appropriate to protect the public health or safety, nor has Petitioner provided any information about such circumstances.

FDA therefore sees no justifiable basis upon which to take any action based on Petitioner's request with respect to the any of the Authorized COVID-19 Vaccines. Accordingly, as noted above, we deny Petitioner's request for FDA to "revoke all EUAs . . . for any COVID vaccine for all demographic groups because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs."

2. Petitioner's Request to Refrain from Granting any Future EUA for a COVID-19 Vaccine for any Population Because Approved Drugs Exist for COVID-19 Prevention

Petitioner also requests in the Petition that FDA "refrain from approving any future EUA . . . for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs."[86] Petition at 1.

Petitioner has provided no evidence that would provide a basis for FDA to conclude that no future COVID-19 vaccine candidate could meet the EUA standard. Indeed, FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition.

Additionally, as explained above in section III.b.i.1.b. of this letter, to the extent Petitioner's contention can be interpreted as an argument that there are FDA-approved drugs indicated for the prevention of COVID-19 (and that therefore the requirement in section 564(c)(3) of the FD&C Act that there is no "adequate, approved, and available alternative" could not be met), this

[85] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12 -15 Years of Age (May 10, 2021), Section 4.6, EUA Prescribing Information and Fact Sheets, https://www.fda.gov/media/148542/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), https://www.fda.gov/media/151613/download; FDA, Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), https://www.fda.gov/media/151611/download.

[86] FDA authorization of an EUA request is not FDA approval. FDA does not "approve" an EUA request. Rather, FDA *authorizes* the emergency use of a product following review of data and information submitted in an EUA request.

argument fails. Should FDA receive future requests for EUAs for COVID-19 vaccine candidates, FDA would consider such requests on a case-by-case basis.[87] Accordingly, Petitioner's request is denied.

3. Petitioner's Request to Refrain from Approving any Future NDA for any COVID-19 Vaccine for any Population

Petitioner's request regarding "any future…NDA … for any COVID Vaccine for all demographic groups" is moot because vaccines are biological products subject to licensure under the PHS Act and are not subject to approval under section 505 of the FD&C Act.

4. Petitioner's Request to Refrain from Licensing any Future BLA for any COVID-19 Vaccine for any Population

Petitioner requests that FDA "refrain from approving any future . . . BLA for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs." Petition at 1. To the extent this request can be interpreted as asserting that the risks of serious adverse events or deaths associated with any COVID-19 vaccine would necessarily outweigh the benefits of any COVID-19 vaccine and therefore FDA should refrain from approving any BLA for any COVID-19 vaccine, this section explains why this argument is unavailing and why we are denying Petitioner's request.

To the extent this request can be interpreted as *also* asserting, in addition to the assertion above, that, because approved drugs provide effective prophylaxis and treatment of COVID-19, the approval of a BLA for a COVID-19 vaccine would be "moot," this section explains why such a position is flawed and why FDA is not granting this request.

a. Petitioner's Request that FDA Refrain from Approving any BLA for any COVID-19 Vaccine because the Current Risks Outweigh the Benefits

Petitioner requests that FDA "refrain from approving any future BLA . . . for any COVID vaccine for all demographic groups" because the risks of serious adverse events or deaths associated with any COVID-19 vaccine outweigh the benefits of any COVID-19 vaccine. Petitioner has provided no evidence that would provide a basis for FDA to conclude that no COVID-19 vaccine could meet the BLA approval standard, however. Indeed, FDA has now approved a BLA for BioNTech's COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) because, among other things, the data and information in the application demonstrated the safety and effectiveness of the vaccine.[88] Thus, Petitioner's request that FDA refrain from approving any BLAs for COVID-19 vaccines is denied.

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[87] FDA has issued guidance describing factors the Agency intends to use in determining how to prioritize EUA requests for COVID-19 vaccine candidates. See October 2020 Guidance at 5 (citing EUA Guidance at 18-20).
[88] See FDA's Summary Basis for Regulatory Action (SBRA) for the BioNTech BLA. This memorandum will be posted on www.fda.gov.

In Appendix I to this letter, we have provided additional background information about FDA's regulatory framework for the review of vaccine BLAs.

b. Petitioner's Request that FDA Refrain from Approving any BLA for any COVID-19 Vaccine because the Current Risks Outweigh the Benefits and because Currently-Approved Drugs are Effective in Preventing COVID-19

To the extent Petitioner is arguing that FDA should *also* refrain from approving a BLA for any COVID-19 vaccine because of the existence of FDA-approved drugs that are effective in preventing COVID-19, this argument is unavailing. As described above in section III.b.i.1, there are no FDA-approved drugs that are effective in preventing COVID-19 (other than BioNTech'sCOVID-19 vaccine [COVID-19 Vaccine, mRNA; Comirnaty], which is now approved for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.).

For the reasons outlined in this section, FDA denies Petitioner's requests to refrain from licensing any BLAs for a COVID-19 vaccine.

ii. Petitioner's Requests Regarding COVID-19 Vaccines in Children

1. Request to Immediately Refrain from Allowing COVID-19 Vaccine Trials to Include Pediatric Subjects

In the Petition, Petitioner requests that FDA "immediately refrain from allowing minors to participate in COVID vaccine trials . . . ." Petition at 1. To the extent that the Petition can be interpreted to request that FDA suspend any COVID-19 vaccine clinical trial that includes pediatric subjects, this section explains why FDA is not at this time ordering that these clinical trials be suspended.

As explained above in section III.a., with certain exceptions, clinical investigations in which a drug is administered to human subjects must be conducted under an IND submitted to FDA by the sponsor. FDA's review of an IND includes a review of the study protocol which describes, among other things, the design of the clinical study, including the identified endpoints and methods for assessing the safety and effectiveness of the investigational product. The Petition requests that FDA adopt a universal approach toward all clinical trials of COVID-19 vaccines. Under FDA's regulations, however, the Agency examines each Investigational New Drug (IND) Application individually and considers the IND in the context of the standards in the regulation.

The FD&C Act provides a specific mechanism, called a "clinical hold," for prohibiting sponsors of clinical investigations from conducting the investigation (section 505(i)(3) of the FD&C Act; 21 U.S.C. 355(i)(3)). FDA's implementing regulations in 21 CFR 312.42 identify the circumstances that may justify a clinical hold. In this section of this letter, we explain why, at this time, FDA has not granted Petitioner's request to place all proposed or ongoing studies of COVID-19 vaccines enrolling pediatric subjects on clinical hold under 21 CFR 312.42(b).

The grounds for placing a proposed or ongoing study, including an ongoing Phase 3 study, on clinical hold are provided in 21 CFR 312.42(b). Specifically, 21 CFR 312.42(b)(1)(i) through (b)(1)(v) provides grounds for imposition of a clinical hold of a Phase 1 study. Additionally, as stated in 21 CFR 312.42(b)(2), FDA may place a proposed or ongoing Phase 2 or 3 investigation on clinical hold if it finds that: (i) any of the conditions in 21 CFR 312.42(b)(1)(i) through (b)(1)(v) apply; or (ii) the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives. As indicated in more detail below, at this time, FDA has not granted Petitioner's request to place all proposed or ongoing studies of COVID-19 vaccines enrolling pediatric subjects on clinical hold under 21 CFR 312.42(b).

- 21 CFR 312.42(b)(1)(i): Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury.

  FDA continues to evaluate all available information and, based on this evaluation thus far, does not believe that human subjects in any COVID-19 vaccine study that includes pediatric subjects are or would be exposed to an unreasonable and significant risk of illness or injury. The Agency reviews the protocols for COVID-19 vaccine clinical trials proposing to enroll pediatric subjects when they are submitted to the IND, in addition to any subsequent protocol amendments. For those clinical trials that have proceeded to studying COVID-19 vaccines in pediatric populations, FDA has determined that, based on all information currently available to FDA, the studies do not expose subjects to unreasonable risks.

- 21 CFR 312.42(b)(1)(ii): The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND.

  The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that clinical investigators named in the IND for any COVID-19 vaccine clinical trial including pediatric subjects are not qualified by reason of their scientific training and experience to conduct the investigation described in the INDs.

- 21 CFR 312.42(b)(1)(iii): The investigator brochure is misleading, erroneous, or materially incomplete.

  The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that the investigator brochures for any ongoing COVID-19 vaccine investigation which includes or proposes to include pediatric subjects are misleading, erroneous, or materially incomplete.

- 21 CFR 312.42(b)(1)(iv): The IND does not contain sufficient information required under 312.23 to assess the risks to subjects of the proposed studies.

  The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that the IND for any ongoing COVID-19 vaccine in which

pediatric subjects are enrolled contains insufficient information required under 21 CFR 312.23 to assess the risks to pediatric subjects participating in the studies.

- 21 CFR 312.42(b)(1)(v) [provides, in part, that]: The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (*i.e.*, affecting reproductive organs) or developmental toxicity (*i.e.*, affecting potential offspring)….

  The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that any COVID-19 vaccine studies enrolling pediatric subjects are excluding from eligibility men or women – including male and female adolescents and teenagers - with reproductive potential.

- 21 CFR 312.42(b)(2)(ii): The plan or protocol for the Phase 2 or Phase 3 investigation is clearly deficient in design to meet its stated objectives.

  The Agency reviewed the protocols for the COVID-19 vaccine investigations involving pediatric subjects at the time they were submitted to the INDs, as well as any subsequent amendments as they were submitted, and has determined that the study designs meets their stated objectives.

  At this time, the Agency is aware of no information to indicate that the protocols for any ongoing clinical investigations of COVID-19 vaccines involving pediatric subjects are clearly deficient in design to meet their stated objectives.

FDA has reviewed the issues raised in the Petition relating to the request to "immediately refrain from allowing minors to participate in COVID vaccine trials." Petition at 1. For the reasons outlined above, and in light of information currently available to FDA, FDA has determined that grounds do not exist to grant Petitioner's request to place all COVID-19 vaccine clinical investigations involving pediatric subjects on clinical hold pursuant to 21 CFR 312.42.

2. Request that FDA Refrain from Issuing EUA Amendments for Authorized COVID-19 Vaccines to Include Indications for Pediatric Populations

The Petition requests, among other things, that "[g]iven the extremely low risk of COVID illness in children, FDA should . . . immediately refrain from amending EUAs to include children. . . ." Petition at 1. To the extent that the Petition requests that FDA refrain from issuing EUA amendments for any of the Authorized COVID-19 Vaccines to include an indication for use in pediatric populations, this section explains why FDA is not granting this request.

In determining whether to issue an EUA for a product, including an amendment to an EUA in order to include additional populations within the indication, the FDA evaluates the available evidence and assesses, among other things, any known or potential risks and any known or potential benefits. Once a manufacturer submits an EUA request for a COVID-19 vaccine, the FDA then evaluates the request and determines whether the relevant statutory criteria are met,

taking into account the totality of the scientific evidence about the vaccine that is available to the agency.

As noted in Section II.b. above, in the October 2020 Guidance, FDA provided recommendations that describe key information that would support issuance of an EUA for a vaccine to prevent COVID-19.[89] In this guidance, FDA explained that, in the case of such vaccines, any assessment regarding an EUA will be made on a case-by-case basis considering the target population, the characteristics of the product, the preclinical and human clinical study data on the product, and the totality of the available scientific evidence relevant to the product.[90] FDA has also stated, in this guidance, that for a COVID-19 vaccine for which there is adequate manufacturing information to ensure its quality and consistency, issuance of an EUA would require a determination by FDA that the vaccine's benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial that demonstrates the vaccine's safety and efficacy in a clear and compelling manner.[91]

a. Information Submitted by Petitioner Regarding the Safety of COVID-19 Vaccines in Pediatric Populations

Petitioner argues that, for children, the risks of COVID-19 vaccines outweigh the benefits because the risk of severe COVID in children is "extremely low." Petition at 1. Petitioner cites to several sources of information in support of this argument (Petition at 12-13), which FDA has reviewed and considered.

Petitioner cites to CDC data[92] regarding death rates of children in the United States due to COVID-19 and compares the number of children who have died involving COVID-19 to the number of Americans of all ages who have died of COVID-19. Petitioner's approach of simply comparing raw numbers of deaths involving COVID-19 in the U.S. pediatric population against the raw numbers of deaths involving COVID-19 in the overall U.S. population (all sexes and all ages), does not provide a sufficient scientific basis upon which to conclude, as Petitioner contends, that the "relative risk for children due to COVID is very low." Petition at 12. Additionally, as discussed in further detail below, based on available data and information, we have concluded that COVID-19 is a serious or life-threatening disease or condition in the 12-17 age group.

As a preliminary matter, we note that petitioner's claim that "the death rate following either vaccination in this age group, assuming these children were trial enrollees, is approximately 2 in 2,000 or 0.1%." (Petition at 13) is erroneous. Our review of the submitted clinical trial data associated with the Pfizer-BioNTech COVID-19 Vaccine has not identified any deaths among adolescent or young adult vaccinees.[93] Additionally, as described in a NEJM article regarding

[89] October 2020 Guidance at 6-7.
[90] Id. at 3.
[91] Id. at 4.
[92] CDC, National Center for Health Statistics, Weekly Updates by Select Demographic and Geographic Characteristics, https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge.
[93] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download (stating that there were two deaths in vaccine recipients, both >55 years of age). FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for

the Moderna COVID-19 vaccine, no deaths were reported among vaccine recipients enrolled in the clinical trial of Moderna COVID-19 Vaccine.[94] Investigational New Drug (IND) application sponsors are required to notify FDA in a written safety report of any adverse experience associated with the use of the drug that is both serious and unexpected.[95] Any death that occurs in a vaccine clinical trial therefore must be reported to FDA and is then thoroughly evaluated by FDA to determine the cause and whether or not the death is plausibly related to the vaccine.

Additionally, we note that Petitioner raised concerns regarding VAERS reports in arguing that COVID-19 vaccines should not be authorized for pediatric populations because, Petitioner argues, "[a]vailable evidence strongly suggests that the vaccine is much more dangerous to children than the disease." Petition at 12. VAERS data reviewed to date has not identified risks related to vaccination that would cause the Agency to change its view that the benefits of vaccination with the Pfizer-BioNTech COVID-19 vaccine outweigh the risks of vaccination in individuals 12-17 years of age. VAERS data is evaluated thoroughly, and as described in greater detail above, FDA acts on safety signals. VAERS reports, however, are not used *in isolation* to draw an association between a vaccine and a possible adverse event.

Finally, we note that petitioner cites to an opinion piece published in the British Medical Journal, which presents the authors' opinion that the benefits of COVD-19 vaccination are outweighed by its risks in pediatric populations.[96] FDA has reviewed this article and determined it does not present evidence that the EUA standard could not be met for pediatric populations. Indeed, as explained in the FDA Decision Memorandum for the Pfizer-BioNTech COVID-19 Vaccine EUA, based on FDA's review of all available data regarding the benefits and risks of the use of the Pfizer-BioNTech COVID-19 vaccine in individuals 12 through 17 years of age, we have determined that this EUA meets the statutory criteria for individuals in this age range.[97]

Petitioner has failed to present data demonstrating that, for children, the risks of COVID-19 vaccines outweigh their benefits because the risk of severe COVID in children is "extremely low." Petition at 1. As explained in this section, the information submitted by Petitioner does not support this contention. As explained in further detail below, data reviewed by the Agency demonstrates that the Pfizer-BioNTech COVID-19 Vaccine, which is authorized for use in individuals 12 years of age and older, continues to demonstrate that the known and potential benefits of this vaccine outweigh its known and potential risks in this population. Any other EUA requests for COVID-19 vaccine candidates for use in pediatric populations will be reviewed on a case-by-case basis under the applicable statutory standards. Therefore, we deny

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Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download (stating that there were no deaths among vaccine recipients 12-15 years of age during the follow-up period).

[94] K. Ali, et al., Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents, NEJM (Aug. 11, 2021), DOI: 10.1056/NEJMoa2109522, https://www.nejm.org/doi/10.1056/NEJMoa2109522.

[95] 21 CFR § 312.32(c)(1)(i).

[96] W. Pegden, V. Prasad, S. Baral, Covid vaccines for children should not get emergency use authorization, BMJ (May 7, 2021), https://blogs.bmj.com/bmj/2021/05/07/covid-vaccines-for-children-should-not-get-emergency-use-authorization/.

[97] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download.

Petitioner's request to refrain from amending any EUA for a COVID-19 vaccine to include a pediatric indication.

3. Request that FDA Immediately Revoke all EUAs for COVID-19 Vaccines with Pediatric Indications

Petitioner requests that FDA "immediately revoke all EUAs that permit vaccination of children under 16 for the Pfizer vaccine and under 18 for other COVID vaccines." Petition at 1. Currently, only the Pfizer-BioNTech COVID-19 vaccine is indicated for the prevention of COVID-19 in pediatric populations. This vaccine is indicated for individuals 12 years of age and older. As explained in section III.B.i.1.b above, in addressing this request, it is necessary to consider the EUA revocation standard provided in section 564(g)(2) of the FD&C Act. In this section, we assess whether any of these statutory conditions under which FDA may revoke an EUA are met with respect to the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA and explain why the EUA revocation standard is not met for this vaccine.

a. Standard for Revocation of EUAs is not Met for the Authorized COVID-19 Vaccines with Pediatric Indications

As explained above in section III.b.i.1.b of this letter, Section 564(g)(2) of the FD&C Act provides the standard for revocation of an EUA. Under this statutory authority, FDA may revise or revoke an EUA if:

> (A) the circumstances described under [section 564(b)(1) of the FD&C Act] no longer exist;
> (B) the criteria under [section 564(c) of the FD&C Act] for issuance of such authorization are no longer met; or
> (C) other circumstances make such revision or revocation appropriate to protect the public health or safety.

As explained above in section II.b., the EUA Guidance notes that once an EUA is issued for a product, in general, that EUA will remain in effect for the duration of the EUA declaration under which it was issued, "unless the EUA is revoked because the criteria for issuance . . . are no longer met or revocation is appropriate to protect public health or safety (section 564(f),(g) [of the FD&C Act])."[98]

i. Circumstances Continue to Justify the Issuance of the EUAs for the Authorized COVID-19 Vaccine with Pediatric Indications

As explained in detail above in section III.b.i.1.b., section 564(b)(2) of the FD&C Act sets forth the statutory standard for termination of an EUA declaration. This provision provides that an EUA declaration remains in place until the earlier of: (1) a determination by the HHS Secretary, in consultation with the Secretary of Defense, that the circumstances that precipitated the declaration have ceased or (2) a change in the approval status of the product such that the authorized use(s) of the product are no longer unapproved. Neither of those statutory criteria is

[98] EUA Guidance at 28.

satisfied with respect to the Authorized COVID-19 Vaccine with a pediatric indication. Thus, the circumstances described under section 564(b)(1) of the FD&C Act continue to exist. FDA therefore is not revoking the EUA for the Authorized COVID-19 vaccine with a pediatric indication under the authority in section 564(g)(2)(A) of the FD&C Act.

1. The Criteria for The Issuance of the Authorized COVID-19 Vaccine with Pediatric Indications Continues to Be Met

This section describes in detail why the criteria under section 564(c) of the FD&C Act continue to be met with respect to the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA and why, therefore, FDA may not revoke this EUA under the authority in section 564(g)(2)(B) of the FD&C Act.

a. Serious or life-threatening disease or condition.

As explained above in section III.b.i.1 of this letter, section 564(c)(1) of the FD&C Act requires that, for an EUA to be issued for a medical product, "the agent(s) referred to in [the HHS Secretary's EUA declaration] can cause a serious or life-threatening disease or condition." FDA has concluded that SARS-CoV-2, which is the subject of the EUA declaration, meets this standard. FDA is not aware of science indicating that there is any change in the ability of the SARS-CoV-2 virus to cause a serious or life-threatening disease or condition, namely COVID-19, nor has Petitioner provided any information about such a change.

The SARS-CoV-2 pandemic continues to present an extraordinary challenge to global health and, as of August 3, 2021, has caused more than 199 million cases of COVID-19 and claimed the lives of more than 4.2 million people worldwide.[99] In the United States, more than 34 million cases and over 611,000 deaths have been reported to the CDC.[100] On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS, and the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Additional background information on the SARS-CoV-2 virus and COVID-19 pandemic may be found in FDA Decision Memoranda for the Authorized COVID-19 Vaccines.[101]

Since March 1, 2020, approximately 1.7 million COVID-19 cases in individuals 12 to 17 years of age have been reported to the Centers for Disease Control and Prevention (CDC). Among these cases approximately 11,700 resulted in hospitalization, with more than 691 ICU admissions

[99] Johns Hopkins University School of Medicine, Coronavirus Resource Center, https://coronavirus.jhu.edu/map.html.
[100] CDC, COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases.
[101] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), https://www.fda.gov/media/146338/download.

and more than 100 deaths. It is difficult to estimate the incidence of COVID-19 among children and adolescents because they are frequently asymptomatic and infrequently tested. Children and adolescents appear less susceptible to SARS-CoV-2 infection and have a milder COVID-19 disease course as compared with adults. However, as with adults, children and adolescents with underlying conditions such as asthma, chronic lung disease, and cancer are at higher risk than their heathier counterparts for COVID-19-related hospitalization and death. Of the children who have developed severe illness from COVID-19, most have had underlying medical conditions. Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious COVID-19-associated condition that can present with persistent fever, laboratory markers of inflammation and heart damage, and, in severe cases, hypotension and shock. As of June 28, 2021, the CDC received reports of 4196 cases and 37 deaths that met the definition for MIS-C.

Both FDA and CDC have convened advisory committee meetings to discuss the use of COVID-19 vaccines in pediatric populations. Overall, these advisory committees agreed that there is a serious risk of severe COVID-19 in the pediatric population. In particular, the June 23, 2021 ACIP meeting discussed the benefits and risks of the use of COVID-19 mRNA vaccines in adolescents and young adults.[102] This discussion raised the point that adolescents and young adults have the highest COVID-19 incidence rates, and that these populations are an increasing proportion of COVID-19 cases reported. COVID-19-associated deaths continue to occur in these populations; since April 2021, 316 deaths have been reported among persons aged 12-29 years. Additionally, post-COVID conditions -- such as Multisystem Inflammatory Syndrome in Children (MIS-C) and Multisystem Inflammatory Syndrome in Adults (MIS-A) -- can occur in these populations following COVID-19.

Therefore, the criterion under section 564(c)(1) continues to be met with respect to the Authorized COVID-19 Vaccines with Pediatric Indications.

b. Evidence of Effectiveness

As explained above in section III.b.i.1.b of this letter, Section 564(c)(2)(A) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2." FDA has determined that based on the totality of scientific evidence available, including data from adequate and well-controlled trials, it is reasonable to believe that the Pfizer-BioNTech COVID-19 vaccine may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition in the 12 through 17 years of age population.[103] The basis for this determination is explained in detail in FDA's decision memoranda regarding

[102] CDC, Megan Wallace and Sara Oliver, CDC ACIP Meeting Presentation, COVID-19 mRNA Vaccines in Adolescents and Young Adults: Benefit-Risk Discussion, (June 23, 2021), https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/05-COVID-Wallace-508.pdf; CDC, ACIP Meeting Slides, (June 23, 2021), https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html.

[103] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download.

the Pfizer BioNTech COVID-19 Vaccine EUA.[104] Section III.b.ii of this letter explains why Petitioner's arguments regarding the effectiveness of the Authorized COVID-19 Vaccines, and the information submitted by Petitioner in support of this argument, does not change FDA's analysis regarding the effectiveness of the Pfizer-BioNTech COVID-19 vaccine in individuals 12 through 17 years of age.

Therefore, the criterion under section 564(c)(2)(A) continues to be met with respect to the Authorized COVID-19 Vaccines.

c. Benefit-Risk Analysis

Section 564(c)(2)(B) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "the known and potential benefits of the product, when used to diagnose, prevent, or treat [the identified serious or life-threatening disease or condition], outweigh the known and potential risks of the product . . . ." Petitioner argues that the current risks of serious adverse events or deaths associated with the authorized COVID-19 vaccines outweigh the benefits of COVID-19 vaccines in the pediatric population. Section III.b.i.1.b.ii above addresses these arguments insofar as they apply to the Authorized COVID-19 Vaccines generally and explains why they are unavailing. Section III.b.ii above addresses Petitioner's arguments regarding the safety of COVID-19 vaccines in the pediatric population, and explains why the information submitted by Petitioner does not change FDA's analysis regarding the benefits and risks of the authorized COVID-19 vaccines in the pediatric population.

d. No Alternatives

Section 564(c)(3) of the FD&C Act provides one of the required statutory factors that must be met in order for a product to be granted an EUA. This statutory provision requires that "there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating [the serious or life-threatening disease or condition]." To the extent Petitioner's contention can be interpreted as an argument that there are FDA-approved drugs indicated for the prevention of COVID-19 in pediatric populations (and that therefore the requirement in section 564(c)(3) of the FD&C Act is not met with respect to the Authorized COVID-19 Vaccine with a pediatric indication), this argument is erroneous.

As described above in section III.b.i.1.b, there are no FDA-approved drugs or biological products indicated to prevent COVID-19 in any population, other than the newly-approved BioNTech COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty). That vaccine is approved for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.[105] The EUA for Pfizer-BioNTech COVID-19 Vaccine remains in effect to cover those 12 through

[104] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download.

[105] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 8-9, https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 9, https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 9, https://www.fda.gov/media/146338/download.

15 years of age, the administration of a third dose to certain immunocompromised individuals 12 years of age and older, and until sufficient approved vaccine can be manufactured and distributed for use in those 16 years of age and older. Similarly, the EUA for the Moderna COVID-19 Vaccine and the Janssen COVID-19 Vaccine remain in effect for individuals 18 years of age and older. Therefore, there is no adequate, approved, and available alternative to the Authorized COVID-19 Vaccines for preventing COVID-19.

ii. No Other Circumstances Make A Revision or Revocation Appropriate to Protect the Public Health or Safety

As noted above in section III.b.i.1.b of this letter, section 564(g)(2)(C) of the FD&C Act provides that FDA may revise or revoke an EUA if circumstances justifying its issuance (under section 564(b)(1)) no longer exist, the criteria for its issuance are no longer met, or other circumstances make a revision or revocation appropriate to protect the public health or safety. The EUA guidance explains that such other circumstances may include:

> significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.[106]

As of the date of this writing, FDA has not identified any such circumstances that would make revocation of the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA appropriate to protect the public health or safety. As stated previously in this response, FDA determined the EUA standard is met for the Pfizer-BioNTech COVID-19 Vaccine in individuals 12 through 17 years of age because data submitted by the sponsors demonstrated in a clear and compelling manner that the known and potential benefits of this vaccine, when used to prevent COVID-19, outweigh the known and potential risks of this vaccine in individuals 12 through 17 years of age, and that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating COVID-19 in this population.

As described in detail in section III.b.i.1 above, FDA has identified circumstances that have made revision of the EUAs for the Authorized COVID-19 Vaccines appropriate, and,

[106] EUA Guidance at 29.

accordingly, has required changes to the authorized labeling for the Authorized COVID-19 Vaccines.[107]

Additionally, as explained above, FDA finds no basis in the information submitted in the Petition, or in any postmarket data regarding the Pfizer-BioNTech COVID-19 Vaccine, to support a revocation of the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA, nor has Petitioner provided any such information in the Petition. FDA is not aware of any information indicating that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine in the 12-17 years of age population are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. Furthermore, there are no other circumstances that make a revision or revocation of the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA appropriate to protect the public health or safety, nor has Petitioner provided any information about such circumstances. FDA therefore sees no justifiable basis upon which to take any action based on Petitioner's request with respect to the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA. Accordingly, as noted above, we deny Petitioner's request that FDA "immediately revoke all EUAs that permit vaccination of children under 16 for the Pfizer vaccine and under 18 for other COVID vaccines." Petition at 1.

iii. Petitioner's Request that FDA Immediately Revoke Tacit Approval that Pregnant Women may Receive any EUA or Licensed COVID-19 Vaccines and Immediately Issue Public Guidance

Petitioner requests that FDA "immediately revoke tacit approval that pregnant women may receive any EUA or licensed COVID vaccines and immediately issue public guidance to that effect." Petition at 1. Because "tacit approval," or revocation thereof, is not a concept that exists in applicable statutes or regulations governing FDA-regulated products, FDA interprets this as a request that the labeling for the Authorized COVID-19 Vaccines, and any COVID-19 vaccine that may be licensed in the future, contain a contraindication for use during pregnancy.
In addressing Petitioner's request for a contraindication, we first discuss the risks posed to pregnant women by COVID-19. We then provide an explanation of the regulatory framework for prescription drug labeling for approved and licensed products, including the standard for inclusion of contraindications in such labeling to inform health care providers of information such as known hazards in the use of a particular drug as well as the requirements for pregnancy and lactation information in such labeling. We then discuss labeling for products made available under an EUA and explain why a contraindication for use in pregnant women was not included in the labeling for the Authorized COVID-19 Vaccines. This section concludes with an explanation for why Petitioner's requests for a contraindication for use during pregnancy in the labeling for the Authorized COVID-19 Vaccines – and BioNTech's COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) - is denied.

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[107] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), https://www.fda.gov/media/148542/download; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), https://www.fda.gov/media/151613/download; FDA, Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), https://www.fda.gov/media/151611/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), https://www.fda.gov/media/146338/download.

1. COVID-19 in Pregnancy

As a preliminary matter, we note that COVID-19 poses significant risks to pregnant women. CDC explains that "observational data regarding COVID-19 during pregnancy demonstrate that pregnant people with COVID-19 have an increased risk of severe illness, including illness resulting in intensive care admission, mechanical ventilation, extracorporeal membrane oxygenation, or death, though the absolute risk for these outcomes is low. Additionally, they are at increased risk of preterm birth and might be at an increased risk of adverse pregnancy complications and outcomes, such as preeclampsia, coagulopathy, and stillbirth."[108]

2. Certain Content and Format Requirements for Prescription Drug Labeling for Products Approved Under NDAs or BLAs

As FDA explains in the draft guidance for industry, Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format, ("Pregnancy and Lactation Guidance") "[p]rescription drug labeling is a communication tool. Its principal objective is to make available to health care providers the detailed prescribing information necessary for the safe and effective use of a drug, in a manner that is clear and useful to providers when prescribing for and counseling patients."[109] In order to achieve this objective, prescription labeling must be based on scientific data, and it must not be inaccurate, false, or misleading.[110]

FDA regulations govern the content and format of prescription drug labeling for approved drugs and biological products (see, e.g., §§ 201.56 and 201.57 (21 CFR 201.57); see also 21 CFR 201.100(c)). The regulations are intended to organize labeling information to more effectively communicate to health care professionals the "information necessary for the safe and effective use of prescription drugs."[111] FDA regulations require that the labeling of most prescription drug products include Highlights of Prescribing Information, which are intended to summarize the information that is most important for prescribing the drug safely and effectively and to facilitate access to the more detailed information within product labeling (see § 201.57(a)). FDA regulations further require that the labeling for most prescription drugs include, among other information, the following sections: Contraindications; Warnings and Precautions; Adverse

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[108] CDC, Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States, Vaccination of Pregnant or Lactating People, https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-product%2Fclinical-considerations.html#pregnant.

[109] Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry, Draft Guidance, July 2020, at 2, https://www.fda.gov/media/90160/download.

[110] 21 CFR § 201.56(a)(2) "The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading."

[111] Preamble to final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922 at 3928, January 24, 2006) (Physician Labeling Rule). For the content and format requirements for the labeling of older prescription drug products that are not subject to the labeling requirements in § 201.57, see § 201.80 (21 CFR 201.80). The specific labeling requirements for older drug products differ in certain respects, and generally are not referenced in this response.

Reactions; and Use in Specific Populations, which includes a subsection on Pregnancy (see § 201.57(c)(1), (5), (6), (7), and (9)(i)).

a. Contraindications

The Contraindications section must describe any situations in which the drug should not be used because the risk of use "clearly outweighs any possible therapeutic benefit" (§ 201.57(c)(5)). This section should include observed and anticipated risks, but not theoretical risks.[112] This could include, for example, a situation where animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrate that the drug has teratogenic effects) and those risks do not outweigh any potential benefit of the drug to any patient.[113]

b. Pregnancy

The Pregnancy subsection is located under the Use in Specific Populations section (see § 201.57(c)(9)(i)). On December 4, 2014, FDA issued a final rule amending the regulations on the requirements for pregnancy and lactation information in prescription drug and biological product labeling (Pregnancy and Lactation Labeling Rule (PLLR)).[114] The PLLR revisions to the regulations were intended "to create a consistent format for providing information about the effects of a drug on pregnancy and lactation that would be useful for decision making by health care providers and their patients."[115] The labeling content and format requirements in § 201.57(c)(9)(i), as revised by the PLLR, took effect on June 30, 2015, with a phased implementation schedule for drugs (including biological products) that are the subject of NDAs, BLAs, and efficacy supplements that had been approved on or after June 30, 2001.[116] The PLLR also requires for all human prescription drug and biological products, including those for which an application was approved before June 30, 2001, that the Pregnancy subsection of labeling be revised to remove the pregnancy letter categories A, B, C, D, and X.[117]
Information in the Pregnancy subsection of labeling may present, in greater detail, a topic that is briefly summarized in another section of labeling (e.g., Warnings and Precautions).[118] FDA has explained that when a topic is discussed in more than one section of labeling, the section containing the most important information relevant to prescribing should typically include a succinct description and should cross-reference sections that contain additional detail.[119]

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[112] See § 201.57(c)(5); see also FDA guidance for industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format; Guidance for Industry, October 2011 (Warnings Guidance), at 8, https://www.fda.gov/media/71866/download.
[113] See Warnings Guidance at 8.
[114] Final rule, "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling" (PLLR) (79 FR 72064, December 4, 2014), https://www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for.
[115] Id. at 72066.
[116] See §§ 201.56(b) and 201.57(c)(9)(i).
[117] §§ 201.57(c)(9) and 201.80; see also 79 FR 72064 at 72095 (December 4, 2014).
[118] PLLR, 79 FR 72064 at 72085 (December 4, 2014).
[119] See FDA guidance for industry, Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements; Guidance for Industry, February 2013, https://www.fda.gov/media/71836/download.

Under current labeling requirements, information in the Pregnancy subsection of labeling is presented under the following subheadings: Pregnancy Exposure Registry; Risk Summary; Clinical Considerations; and Data.[120] The labeling for the Authorized COVID-19 Vaccines includes the Pregnancy Exposure Registry and the Risk Summary subheadings. We briefly describe these subheadings below.

i. Pregnancy Exposure Registry

If there is a scientifically acceptable pregnancy exposure registry for the drug, the labeling must state that fact and provide contact information needed for enrolling in or obtaining information about the registry.

ii. Risk Summary

The Risk Summary subheading is required under the Pregnancy subsection because certain statements must be included even when no product-specific data are available, given that all pregnancies have a background risk of birth defect, loss, or other adverse outcomes.[121] The Risk Summary must contain risk statement(s) that describe for the drug the risk of adverse developmental outcomes based on all relevant human data, animal data, and/or the drug's pharmacology.[122] When multiple data sources are available, the risk statements are required to be presented in the following order: human, animal, and pharmacologic.[123]

When human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, a risk statement based on human data must summarize the specific developmental outcome(s) and include its incidence and the effects of dose, duration of exposure, and gestational timing of exposure.[124] If human data indicate that there is an increased risk for a specific adverse developmental outcome in infants born to women exposed to the drug during pregnancy, the risk summary must contain a quantitative comparison of that risk to the risk for the same outcome in infants born to women who were not exposed to the drug, but who have the disease or condition for which the drug is indicated to be used.[125] When risk information is not available for women with the disease or condition(s) for which the drug is indicated, the risk summary must contain a comparison of the specific outcome in women exposed to the drug during pregnancy against the rate at which the outcome occurs in the general population.[126]

When animal data are available, the risk statement based on such data must describe the potential risk for adverse developmental outcomes in humans and summarize the available data.[127] This statement must include: the number and type(s) of species affected; timing of exposure; animal doses expressed in terms of human dose or exposure equivalents; and outcomes for pregnant animals and offspring.[128]

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[120] § 201.57(c)(9)(i).
[121] § 201.57(c)(9)(i)(B).
[122] Id.
[123] Id.
[124] § 201.57(c)(9)(i)(B)(1).
[125] Id.
[126] Id.
[127] § 201.57(c)(9)(i)(B)(2).
[128] Id.

With respect to pharmacology, when the drug has a well-understood pharmacologic mechanism of action that may result in adverse developmental outcomes, the Risk Summary must explain the mechanism of action and the potential associated risks.[129]

3. Inclusion of Contraindications and Pregnancy Information in the Labeling for the Authorized COVID-19 Vaccines

For the emergency use of an unapproved product, section 564(e)(1)(A)(i) of the FD&C Act requires that FDA must—to the extent practicable given the applicable circumstances of the emergency, and as FDA finds necessary and appropriate to protect the public health—establish appropriate conditions designed to ensure that health care professionals administering the authorized product are informed:

- That FDA has authorized the emergency use of the product (including the product name and an explanation of its intended use);
- Of the significant known and potential benefits and risks of the emergency use of the product, and the extent to which such benefits and risks are unknown; and
- Of available alternatives and their benefits and risks.

Therefore, as explained in the EUA Guidance, FDA recommends that "a request for an EUA include a 'Fact Sheet' for health care professionals or authorized dispensers that includes essential information about the product. In addition to the required information, Fact Sheets should include . . . any contraindications or warnings."[130] The EUA guidance also recommends that, for unapproved drugs that do not have "FDA-approved labeling for any indication . . . in addition to the brief summary information found in a Fact Sheet, the sponsor also develop more detailed information similar to what health care professionals are accustomed to finding in FDA-approved package inserts."[131]

The sponsors for all the Authorized COVID-19 Vaccines submitted such prescribing information in the EUA requests, and FDA reviewed and authorized this labeling. The Fact Sheets for Healthcare Providers Administering Vaccine for all of the Authorized COVID-19 Vaccines contain Contraindications and Warnings and Precautions sections because FDA determined that sufficient data existed for inclusion of such information in the authorized labeling for these vaccines.[132]

FDA did not, however, require inclusion of a contraindication for pregnancy in the authorized labeling. The authorized COVID-19 vaccines are authorized for use in an age range that includes women of childbearing age and are not contraindicated for use in pregnant women because FDA

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[129] § 201.57(c)(9)(i)(B)(3).
[130] EUA Guidance at 22.
[131] EUA Guidance at 23.
[132] Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Sections 5.2 and 5.3 Warnings and Precautions Regarding Thrombosis with Thrombocytopenia and GBS, https://www.fda.gov/media/146304/download; Pfizer-BioNTech COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, https://www.fda.gov/media/144413/download Moderna COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, https://www.fda.gov/media/144637/download.

is not aware of any evidence that suggests the risk of use of the Authorized COVID-19 Vaccines in pregnant women would clearly outweigh any possible therapeutic benefit.[133] Nor has the Petitioner presented any such evidence in the Petition. Accordingly, this request is denied.

4. Inclusion of Contraindications and Pregnancy Information in the Labeling for Licensed COVID-19 Vaccines

With respect to Petitioner's request that FDA "immediately revoke tacit approval that pregnant women may receive any EUA or licensed COVID vaccines and immediately issue public guidance to that effect" (Petition at 1; emphasis added), as explained above in this section, FDA regulations require the Contraindications section of the labeling for an approved drug or biological product to describe any situations in which the drug or biological product should not be used because the risk of use "clearly outweighs any possible therapeutic benefit" (§ 201.57(c)(5)). This section should include observed and anticipated risks, but not theoretical risks.[134] The approved COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) is indicated for use in an age range that includes women of childbearing age and is not contraindicated for use in pregnant women because FDA is not aware of any evidence that suggests the risk of use of BioNTech's COVID-19 vaccine in pregnant women would clearly outweigh any possible therapeutic benefit,[135] nor has the Petitioner presented any such evidence in the Petition.

In its review of a BLA for any future COVID-19 vaccine candidate, FDA will apply the regulatory standards outlined above in determining, on a case-by-case basis, whether to include a contraindication in pregnancy, or any other contraindications, in the approved labeling for such a vaccine. Accordingly, Petitioner's request is denied.

iv. Petitioner's Request that FDA Immediately Amend its Guidance regarding Certain Approved Drugs [chloroquine drugs, ivermectin, "and any other drugs demonstrated to be safe and effective against COVID"]

Petitioner requests that the Agency "immediately amend its existing guidance for the use of the chloroquine drugs, ivermectin, and any other drugs demonstrated to be safe and effective against COVID, to comport with current scientific evidence of safety and efficacy at currently used doses and immediately issue notifications to all stakeholders of this change." Petition at 2. FDA has not issued "guidance for the use of chloroquine drugs, ivermectin, and other drugs

[133] FDA's decision memoranda for the Authorized COVID-19 Vaccines discuss FDA's analysis of all available data regarding the use of the Authorized COVID-19 Vaccines in pregnancy. *See*, FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), https://www.fda.gov/media/144416/download; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), https://www.fda.gov/media/144673/download; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), https://www.fda.gov/media/146338/download.

[134] See § 201.57(c)(5); see also Warnings Guidance at 8.

[135] See FDA's Summary Basis for Regulatory Action (SBRA) for the BioNTech BLA. This memorandum will be posted on www.fda.gov.

demonstrated to be safe and effective against COVID."[136] FDA has, however, analyzed adverse event information and made publicly available safety issues regarding the use of hydroxychloroquine and chloroquine to treat patients with COVID-19.[137] FDA has also informed the public that it has received multiple reports of patients who have required medical support and been hospitalized after self-medicating with ivermectin intended for horses, that taking large doses of ivermectin can cause serious harm, that ivermectin is not authorized or approved by FDA to treat COVID-19, and that using any treatment for COVID-19 that is not approved or authorized by the FDA, unless part of a clinical trial, can cause serious harm.[138] You have not provided any evidence to suggest that the safety information in these communications is inaccurate. Thus, to the extent you are requesting that FDA withdraw or revise these previous safety communications, that request is denied.

v. Petitioner's Request that FDA Issue Guidance to the Secretary of Defense and the President

Petitioner requests that FDA "issue guidance to the Secretary of the Defense and the President not to grant an unprecedented Presidential waiver of prior consent regarding COVID vaccines for Servicemembers under 10 U.S.C. § 1107(f) or 10 U.S.C. § 1107a." Petition at 2.

FDA denies this request because FDA, an agency within the U.S. Department of Health and Human Services, does not issue guidance of the type requested to the President of the United States or to other Departments in the executive branch of the U.S. federal government.

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[136] Under FDA's good guidance practices regulations, a "guidance document" is defined as "documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue." 21 CFR 10.115(a)(b)(1). The regulation provides further that "[g]uidance documents include, but are not limited to, documents that relate to: The design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement policies." Importantly, the provision at 21 CFR 10.115(b)(3), excludes from the definition of "guidance document" general information documents provided to consumers or health professionals, such as those communications that have been provided to the public regarding the use of hydroxychloroquine, chloroquine, and ivermectin to treat patients with COVID-19. 21 CFR 10.115(b)(3) states: "[g]uidance documents do not include: Documents relating to internal FDA procedures, agency reports, general information documents provided to consumers or health professionals, speeches, journal articles and editorials, media interviews, press materials, warning letters, memoranda of understanding, or other communications directed to individual persons or firms." (Emphasis added.)

[137] FDA Drug Safety Communication, FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems, April 24, 2020, updated June 15, 2020 and July 1, 2020, https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or; FDA, CDER Office of Surveillance and Epidemiology Pharmacovigilance Memorandum, May 19, 2020, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/OSE%20Review_Hydroxychloroquine-Cholorquine%20-%2019May2020_Redacted.pdf.

[138] FDA Consumer Update, Why You Should Not Use Ivermectin to Treat or Prevent COVID-19, March 5, 2021, https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19; FDA Letter to Stakeholders, Do Not Use Ivermectin Intended for Animals as Treatment for COVID-19 in Humans, April 10, 2020, https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-covid-19-humans.

vi. Petitioner's Request that FDA Issue Guidance to Stakeholders Regarding the Option to Refuse or Accept Administration of Investigational COVID-19 Vaccines

Petitioner requests that FDA "issue guidance to all stakeholders in digital and written formats to affirm that all citizens have the option to accept or refuse administration of investigational COVID vaccines without adverse work, educational or other non-health related consequences, under 21 U.S.C. § 360bbb-3(e)(1)(a)(ii)(III) 1 and the informed consent requirements of the Nuremberg Code."[139] We interpret this request to relate to the Authorized COVID-19 Vaccines and third parties' decisions with respect to unvaccinated individuals' participation in certain activities. Such decisions by third parties with respect to employment, education, and other non-FDA-regulated activities would not be within FDA's purview. Accordingly, FDA denies Petitioner's request.

vii. Petitioner's Request that FDA Issue Guidance Regarding Marketing and Promotion of COVID-19 Vaccines

FDA notes that your Petition discusses statements made by CDC. For requests intended for CDC, you should contact CDC directly.

As explained above in section III.b.i.1.b of this response, the EUA revocation standard in section 564(g)(2) of the FD&C Act is not met for any of the Authorized COVID-19 Vaccines. With respect to Petitioner's request to issue guidance pending revocation of the EUAs for the Authorized COVID-19 Vaccines, we note that the EUA Guidance contains a section regarding advertising for EUA products. As explained in the EUA guidance, FDA may, under section 564(e)(1)(B) of the FD&C Act, on a case-by-case basis and to the extent feasible given the circumstances of a particular public health emergency, establish certain additional conditions that FDA finds to be necessary or appropriate to protect the public health.[140] The EUA guidance explains that, under section 564(e)(4) of the FD&C Act, FDA may place conditions on "advertisements and other promotional descriptive printed matter (e.g., press releases issued by the EUA sponsor) relating to the use of an EUA product, such as requirements applicable to prescription drugs under section 502(n) . . . ."[141] FDA's authority under section 564(e)(4) ordinarily does not extend to statements by third parties who have no direct connection with the EUA sponsor.

For the Authorized COVID-19 Vaccines, FDA has determined that such conditions are necessary to protect the public health. Accordingly, the Letter of Authorization for each of the Authorized COVID-19 Vaccines contains conditions related to printed matter, advertising, and promotion.[142] Given the current public health emergency, FDA does not see a need to expend the resources

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[139] Concerns about potential State vaccine requirements are better directed to the States. FDA does not mandate use of vaccines.
[140] EUA Guidance at 26.
[141] Id. at 27.
[142] FDA, Pfizer-BioNTech COVID-19 Vaccine Letter of Authorization (Aug. 12, 2021), https://www.fda.gov/media/150386/download; FDA, Moderna COVID-19 Vaccine Letter of Authorization (Aug. 12, 2021), https://www.fda.gov/media/144636/download; FDA, Janssen COVID-19 Vaccine Letter of Authorization (June 10, 2021), https://www.fda.gov/media/146303/download.

necessary to develop and issue additional guidance on this topic. Thus, because FDA has already issued guidance addressing advertising and promotion of EUA products, and because FDA has established conditions related to printed matter, advertising, and promotion for all of the Authorized COVID-19 Vaccines, FDA denies Petitioner's request to issue additional guidance on this issue.

c. Conclusion

FDA has considered Petitioner's requests as they relate to the Authorized COVID-19 Vaccines and the approved COVID-19 Vaccine. For the reasons given in this letter, FDA denies the requests in Petitioner's citizen petition. Therefore, we deny the Petition in its entirety.

Sincerely,

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

cc: Dockets Management Staff

Appendix I: Aspects of Vaccine Development and Process for Licensure

A. Vaccines are Biologics and Drugs

Vaccines are both biological products under the Public Health Service Act (PHS Act) (42 U.S.C. § 262) and drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 321). The PHS Act defines a "biological product" as including a "vaccine…or analogous product…applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1). The FD&C Act defines drug to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man." 21 U.S.C. § 321(g)(1)(B).

Under the PHS Act, a biological product may not be introduced or delivered for introduction into interstate commerce unless a biologics license is in effect for the product. 42 U.S.C. § 262(a)(1)(A).

B. Clinical Investigations of Vaccines

Before a vaccine is licensed (approved) by FDA and can be used by the public, FDA requires that it undergo a rigorous and extensive development program that includes laboratory research, animal studies, and human clinical studies to determine the vaccine's safety and effectiveness.

The PHS Act and the FD&C Act provide FDA with the authority to promulgate regulations that provide a pathway for the study of unapproved new drugs and biologics. 42 U.S.C. § 262(a)(2)(A) and 21 U.S.C. § 355(i). The regulations on clinical investigations require the submission of an Investigational New Drug application (IND), which describes the protocol, and, among other things, assures the safety and rights of human subjects. These regulations are set out at 21 CFR Part 312. See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).

The regulations provide that, once an IND is in effect, the sponsor may conduct a clinical investigation of the product, with the investigation generally being divided into three phases. With respect to vaccines, Phase 1 studies typically enroll fewer than 100 participants and are designed to look for very common side effects and preliminary evidence of an immune response to the candidate vaccine. Phase 2 studies may include up to several hundred individuals and are designed to provide information regarding the incidence of common short-term side effects, such as redness and swelling at the injection site or fever, and to further describe the immune response to the investigational vaccine. If an investigational new vaccine progresses past Phase 1 and Phase 2 studies, it may progress to Phase 3 studies. For Phase 3 studies, the sample size is often determined by the number of subjects required to establish the effectiveness of the new vaccine, which may be in the thousands or tens of thousands of subjects. Phase 3 studies are usually of sufficient size to detect less common adverse events.

If product development is successful and the clinical data are supportive of the proposed indication, the completion of all three phases of clinical development can be followed by submission of a Biologics License Application (BLA) pursuant to the PHS Act (42 U.S.C. § 262(a)), as specified in 21 CFR § 601.2.

C. Biologics License Applications

A BLA must include data demonstrating that the product is safe, pure, and potent and that the facility in which the product is manufactured "meets standards designed to assure that the biological product continues to be safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i). FDA does not consider an application to be filed until FDA determines that all pertinent information and data have been received. 21 CFR § 601.2. FDA's filing of an application indicates that the application is complete and ready for review but is not an approval of the application.

Under § 601.2(a), FDA may approve a manufacturer's application for a biologics license only after the manufacturer submits an application accompanied by, among other things, "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency." The BLA must provide the multidisciplinary FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc.) with the Chemistry, Manufacturing, and Controls (CMC)[143] and clinical information necessary to make a benefit-risk assessment, and to determine whether "the establishment(s) and the product meet the applicable requirements established in [FDA's regulations]." 21 CFR § 601.4(a).

FDA generally conducts a pre-license inspection of the proposed manufacturing facility, during which production of the vaccine is examined in detail. 42 U.S.C. § 262(c). In addition, FDA carefully reviews information on the manufacturing process of new vaccines, including the results of testing performed on individual vaccine lots.

FDA scientists and physicians evaluate all the information contained in a BLA, including the safety and effectiveness data and the manufacturing information, to determine whether the application meets the statutory and regulatory requirements. FDA may also convene a meeting of its advisory committee to seek input from outside, independent, technical experts from various scientific and public health disciplines that provide input on scientific data and its public health significance.

As part of FDA's evaluation of a vaccine as a whole, FDA takes all of a vaccine's ingredients into account (including preservatives and adjuvants). FDA licenses a vaccine only after the Agency has determined that the vaccine is safe and effective for its intended use, in that its benefits outweigh its potential risks.

[143] Also referred to as Pharmaceutical Quality/CMC.

Marks Decl. Exhibit F

July 23, 2021

Electronic Submission

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

This petition for administrative action is submitted on behalf of CAALM, the Coalition Advocating for Adequately Licensed Medicines ("Petitioner") pursuant to 21 C.F.R. § 10.30 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act to request that the Commissioner of Food and Drugs (the "Commissioner") require that the vaccine manufacturers provide the FDA with the data outlined in the "Actions Requested" section below before approval of any COVID-19 vaccine.

The Food and Drug Administration (FDA) has granted Emergency Use Authorizations (EUAs) to three COVID-19 vaccines, enabling rapid, and widespread vaccine rollout across the United States. These EUAs do not have any built-in expiration date, and therefore vaccines can continue to be lawfully distributed under EUA even after a future date when a public health emergency no longer exists.

Approximately seven months have passed since the first EUAs were granted, and two vaccine manufacturers now seek licensure (approval) and have submitted Biologics License Applications (BLAs). Other manufacturers have indicated similar intentions, as well as intentions for EUAs for additional pediatric populations.

We believe the FDA should not prematurely grant a license to any COVID-19 vaccine until all necessary efficacy and safety studies are completed and substantial evidence demonstrates the benefits of an individual COVID-19 vaccine product outweigh the harms for the indicated, recipient population. We are concerned that the premature licensure of a COVID-19 vaccine can seriously undermine public confidence in regulatory authorities, particularly if long-term safety issues were to emerge following licensure.

In this petition, we outline **efficacy and safety measures that must be met before serious consideration is given to granting a BLA of any COVID-19 vaccine**. These measures include:

1. **Completing at least 2 years of follow-up** of participants originally enrolled in pivotal clinical trials, even if the trials were unblinded and now lack a placebo control. All vaccine manufacturer phase 3 trials were already designed with this planned duration.

2. Ensuring, prior to including in the list of populations for which a vaccine is approved, that there is **substantial evidence of clinical effectiveness that outweighs harms in special populations** such as: infants, children, and adolescents; those with past SARS-CoV-2 infection; immunocompromised; pregnant women; nursing women; frail older adults; and individuals with cancer, autoimmune disorders, and hematological conditions.
3. Requiring thorough **safety assessment of spike proteins** being produced in-situ by the body tissues following vaccine administration, and spike proteins' full biodistribution, pharmacokinetics, and tissue specific toxicity.
4. Completion of **vaccine biodistribution studies** from administration site and safety implications of mRNA translation in distant tissues.
5. **Thorough investigation of all severe adverse reactions reported following COVID-19 vaccination**, such as deaths, reported in the United States and global pharmacovigilance systems.
6. Assessment of **safety in individuals receiving more than two doses.**
7. **Inclusion of gene delivery and therapy experts in the Vaccines and Related Biological Products Advisory Committee (VRBPAC)**, in recognition of the fact that the novel COVID vaccines work on the premise of gene delivery, in contrast to conventional vaccines.
8. **Enforcing stringent conflict of interest requirements** to ensure individuals involved in data analysis and BLA-related decision making processes have no conflict of interests with vaccine manufacturers.

A COVID-19 vaccine BLA should be approved when—and only when—substantial evidence demonstrates the benefits of a specific product outweigh the harms for the indicated, recipient population.

This means that the following are **invalid reasons** to approve a COVID-19 vaccine:

- **To ensure vaccines are accessible after the public health emergency has ended.** COVID-19 vaccines granted an emergency use authorization (EUA) can be lawfully used after the expiry of the SARS-CoV-2 public health emergency declaration. (This is made clear by the many products for Ebola and Zika viruses which still have active EUAs.[1])

- **To ensure adequate access to vaccines across the population.** A BLA is not necessary to assure access to COVID-19 vaccines. Unlike normal licensing, in which widespread use of a drug or vaccine follows approval, EUAs for COVID-19 vaccines have enabled, and continue to enable, their widespread use. Ensuring access to vaccines is irrelevant to the considerations for issuance of a BLA because broad access to COVID-19 vaccines has already been accomplished.

- **To enable vaccine mandates.** Consideration of vaccine mandates is outside of FDA's purview. Furthermore, a mandate should only be considered once the evidentiary conditions are met for a BLA (demonstrating that benefits outweigh harms).

- **To bolster public confidence.** Like mandates, approving a medical product in order to bolster public confidence is backward logic and is outside the FDA's purview. Approving before substantial evidence that population-based evidence of clinical effectiveness is superior to harms may contribute to public wariness and hesitancy, not only about COVID-19 vaccines, but other vaccines and public health authorities more broadly. An approval may bolster public confidence, but it is not a valid reason to approve.

Regardless of any legitimacy of each of the above reasons, none provides grounds to approve a COVID-19 vaccine.

The widespread use of a COVID-19 vaccine under EUA, particularly for a limited amount of time, also is not a valid reason to approve a product. Even if vaccine recipients are followed up within observational studies, such studies may have important design biases and flaws, and their conclusions, especially concerning clinical effectiveness outcomes, may not be reliable.

Premature FDA approval of any COVID-19 vaccine could negatively impact the health and safety of US residents, with global ramifications considering the international importance of FDA decisions. It also could set a precedent of lowered standards for future vaccine approvals. For these reasons and due to the compelling need to ensure the safety and efficacy of any COVID-19 vaccine licensed by the FDA and to allow Petitioner the opportunity to seek emergency judicial relief should the instant Petition be denied, it is respectfully requested that FDA act on the instant Amended Petition by July 30, 2021.

I. ACTIONS REQUESTED

Petitioner request that the FDA, prior to granting any license for a COVID-19 vaccine:

1. Confirm, in revised Guidance, that the FDA expects a minimum of 2 years of follow-up of participants enrolled in pivotal clinical trials, even if trials are unblinded and lack a placebo control.

2. Require data demonstrating substantial evidence of clinical effectiveness that outweighs harms, in all special populations, as a condition of consideration of including these populations among the indicated populations. Special populations include: infants, children, and adolescents; those with past SARS-CoV-2 infection; immunosuppressed individuals; those with history of or current cancer; individuals with hematological disorders or autoimmune diseases; pregnant or nursing women; and frail older adults.

3. Require data on the safety and pharmacokinetic profiles of the spike protein.

4. Require data from biodistribution studies investigating the actual COVID-19 vaccines.

5. Require data from pharmacovigilance systems in the US and globally documenting a thorough investigation of serious adverse events, carried out by independent, impartial individuals.

6. Clarify in revised Guidance that safety data from individuals receiving more than 2 vaccine doses must be submitted.

7. Ensure the inclusion of experts in gene therapy in the VRBPAC.

8. Ensure that the analysis of data and decisions regarding any COVID-19 vaccine BLA application are informed by experts with no financial or research relationships with any vaccine manufacturers within the last 36 months, both within FDA and amongst the composition of the VRBPAC.

II. STATEMENT OF GROUNDS

Here, in the order as above, we set out the rationale for each requested action.

1. **Confirm, in revised Guidance, that the FDA expects a minimum of 2 years of follow-up of participants enrolled in pivotal clinical trials, even if trials are unblinded and lack a placebo control. Rationale:**
    a. Requiring at least 2 years is consistent with the 2 year follow-up duration prospectively proposed by the manufacturers when they registered their ongoing phase 3 trials of COVID-19 vaccines (Moderna: NCT04470427, Pfizer: NCT04368728, Janssen: NCT04505722) and consistent with the June 2020 FDA guidance on COVID-19 vaccines which stated participants should be followed for COVID-19 outcomes for "as long as feasible, ideally at least one to two years."[2]
    b. Important adverse event signals can be detected in clinical trials. This is true despite enrolling tens of thousands of participants, which is still too few to assess rare adverse events. For example, a serious blood clot occurring in the phase 3 Janssen clinical trial led to an initial trial pause in October 2020.[3]
    c. Two year follow-up from trials allows the detection of commonly experienced longer-term adverse effects that may not manifest until many months following vaccination.
    d. Two year follow-up from trials would also allow for more detailed assessment of infection, re-infection, infectiousness, and the monitoring of immune response over time, among all vaccinated participants.
    e. The quality of data collection in clinical trials can be expected to be superior to passive data collection systems like the Vaccine Adverse Event Reporting System (VAERS). Therefore, trials of at least 2 years duration provide a valuable chance to develop a more complete understanding of the adverse event profile in the general population as well as in specific groups, such as individuals of

reproductive age, immunocompromised individuals, and different age groups, including adolescents and young children.

f. The quality of data on adverse events during an ongoing trial can be improved while the trial is ongoing (e.g., improving the range of types of adverse events that are systematically assessed), as and when evidence from other data sources (e.g., pre-clinical or pharmacovigilance) show any trends or indicate specific types of adverse events of special interest.

g. Finally, the expectation of at least 2 years of follow-up prior to BLA also carries the advantage of longer-term data collection from other available sources (e.g., MedWatch/VAERS, V-safe, Vaccine Safety Datalink, FDA-CMS, BEST & PRISM, VA Electronic Health Records & data warehouse, Department of Defense DMSS, and Genesis HealthCare (Brown University & NIH-National Institute of Aging), as well as other medical claims databases).

2. **Require data demonstrating substantial evidence of clinical effectiveness that outweighs harms, in all special populations, as a condition of consideration of including these populations among the indicated populations. Special populations include: infants, children, and adolescents; those with past SARS-CoV-2 infection; immunosuppressed individuals; those with history of or current cancer; individuals with hematological disorders or autoimmune diseases; pregnant or nursing women; and frail older adults. Rationale:**

   a. The efficacy and safety of medicines often differs amongst populations such as healthy young adults vs. older adults, men vs. women, or SARS-CoV-2 survivors vs. never-exposed individuals.

   b. For example, the relative risks of SARS-CoV-2 infection, hospitalization, and death are considerably lower in infants, children, and adolescents in comparison to adults.[4,5]

   c. For example, individuals who experienced past SARS-CoV-2 infection (which are now believed to be a significant minority of many subpopulations[6]) are likely to have immunity to subsequent infections for as long or longer than immunity conferred by vaccine,[7–10] and may also be at heightened risk for adverse effects.[11–14]

   d. The ongoing phase 3 trials of COVID-19 vaccines (Moderna: NCT04470427, Pfizer: NCT04368728, Janssen: NCT04505722) largely (or wholly) excluded the following important populations in which there is reason to believe the effects of the product may differ from the populations enrolled in the trial:

      i. Infants, children, and adolescents
      ii. Those with past SARS-CoV-2 infection
      iii. Those who are immunosuppressed
      iv. Those with history of or current cancer
      v. Those with hematological disorders
      vi. Those with autoimmune diseases
      vii. Those who are pregnant or nursing
      viii. Frail older adults (including those living in nursing homes)

e. The question is not simply whether there is efficacy, but how much efficacy exists in these populations, what kind of efficacy (e.g. reduction in risk of symptomatic COVID-19 vs. reduction in risk of hospitalization or death), and do efficacy advantages outweigh potential harms in these populations.
f. Before these special populations can be considered for inclusion amongst the approved indicated populations, data demonstrating substantial evidence of clinical effectiveness that outweighs harms in these specific populations, are needed.

3. **Require data on the safety and pharmacokinetic profiles of the spike protein.**
Rationale:
   a. In-situ production of SARS-CoV-2 spike protein is the target mechanism of action of all COVID-19 vaccines with an EUA at present. Therefore, the safety profile of spike protein itself (i.e., in the absence of virus) must be thoroughly understood in the range of populations on the indications list.
   b. Recently, evidence of systemic circulation of spike protein or its components in subjects post-immunization was reported.[15] All studies we are aware of to date raise concerns about the safety of spike protein,[16–28] and the concentration of circulatory spikes was correlated to the disease severity in COVID-19 patients.[29]
   c. Required studies must, at a minimum, address these concerns:
      i. Coagulopathy issues, including blood clots, hemorrhage, thrombocytopenia, heart attack, and strokes. According to the VAERS, as of May 21, 2021, there have been a total of 1,222 reports of thrombocytopenia/low platelets; and 6,494 (112 in 0-24 year-olds) reports of blood clots/strokes.
      ii. Reproductive issues, including menstrual irregularities, reduced fertility, miscarriages, and preterm births. According to VAERS, as of May 21, 2021, there were 511 reports of miscarriage and 522 reports of uterine hemorrhage (including 88 in women older than 50 years). The vaccines induce the generation of antibodies to attack spike protein, which are genetically similar to proteins produced by the placenta.[30] To date, no vaccine sponsors have conducted immunologic studies of spike protein involvement with proteins involved in placental development.
      iii. Carcinogenesis. There is preliminary and theoretical evidence that the spike protein may promote cancer.[31,32] Considering the potential for annual booster vaccinations, COVID-19 vaccines should be treated similarly to medication taken for chronic conditions on a long term basis. Carcinogenic potential is important to characterize.
      iv. Transmission of spike protein (or its fragments) from vaccinated individuals, such as through breast milk and associated risk in neonates and infants. According to the UK Medicines & Healthcare products Regulatory Agency, there are 921 reports of exposure via breast milk following AstraZeneca's vaccine and 215 reports following Pfizer's vaccine.

v. Neurological disorders, including Guillain-Barré syndrome, acute disseminated encephalomyelitis, transverse myelitis, encephalitis, myelitis, encephalomyelitis, meningoencephalitis, meningitis, encephalopathy, demyelinating diseases, and multiple sclerosis.
vi. Cardiac issues, including myocardial infarction, myocarditis and pericarditis, among others. According to the VAERS, as of May 21, 2021, there have been a total of 1,598 reports of heart attacks (24 reported in 0-24 year-olds; 501 resulted in death).
vii. Autoimmune diseases, including thyroiditis and diabetes mellitus, immune thrombocytopenia, autoimmune hepatitis, primary biliary cholangitis, systemic sclerosis, autoimmune disease for skeletal muscles (myasthenia gravis, myositis such as polymyositis, dermatomyositis, or other inflammatory myopathies)
viii. Studies should be conducted in individuals of both sexes[33] and all ages. We cannot assume that the effects of spike protein are the same across populations of all ages, sex, and across pre-existing conditions.

4. **Require data from biodistribution studies investigating the actual COVID-19 vaccines. Rationale:**
   a. Data from the biodistribution studies submitted by Moderna and Pfizer suggests that the vaccines distribute widely in the body, including to the liver, brain, heart, lung, adrenals, ovaries, and testes, among many other tissues.[34,35] (**See Tables 1a, 1b, and 2 below for studies R-[?]-0072 and 185350 submitted by Pfizer and study 5002121 submitted by Moderna.**)
   b. However these were not studies of the currently authorized products: Pfizer's BNT162b2, Moderna's mRNA-1273, or Janssen's Ad26.COV2.S.[34–36]
   c. Instead of presenting novel biodistribution studies of the COVID-19 vaccine formulations, sponsors presented substitute studies to FDA for an EUA during the pandemic.[34–36]
   d. Therefore, novel biodistribution studies investigating the actual COVID-19 vaccines are necessary.
   e. Biodistribution studies would be required for any small molecule pharmaceutical drug submitted for approval (i.e. New Drug Application), and should be conducted on the COVID-19 vaccines as well as these novel vaccines which work on the premise of gene delivery--very different to conventional vaccines.
   f. Biodistribution studies help inform an understanding of vaccine transfection to various tissues (away from injection site) spurring various distant tissues to produce spike proteins and consequent autoimmune response against the body's cells. These studies will therefore help enhance our understanding of the nature of potential short and long term adverse events. At this point in time, in which other data sources exist to characterize short term harms of COVID-19 vaccines with an EUA, the utility of biodistribution studies to characterize long term adverse effects and better understand potential mechanism(s) of action of short and long term harms, remains critically important.

g. Necessary studies must, at a minimum, address these concerns related to biodistribution, as well as the effects of vaccines in the body:
    i. The need to know basic pharmacokinetic parameters, including absorption, distribution, metabolism, and excretion (ADME).
    ii. Effects of multiple doses. ADME may change depending on dose and cumulative dose and should be investigated. This is more important than usual as the whole purpose of all COVID-19 vaccines with an EUA at present is to change the body's way of processing spike protein, and therefore repeated injections should result in different rates of clearance of spike protein from the blood, and different rates of immune attack on spike protein producing cells.
    iii. The impact of body mass index (size of deltoid muscle) and vaccine distribution away from injection site, implications for dose estimation for lean or younger age groups or frail older adults.
    iv. The duration of the studies must be sufficient to fully understand the complete distribution and elimination of the injected vaccine and its carrier and other constituents. For example, data from the substitute study submitted for Pfizer's vaccine (**see Tables 1a, 1b, and 2 below for studies R-[?]-0072 and 185350 submitted by Pfizer and study 5002121 submitted by Moderna**) showed levels of drug product increasing at the 48 hour mark, but it is unknown what occurred after 48 hours as this was apparently the study cut off.[37]
    v. Potential side effects (safety review) in those organs/tissues with a detectable proportion of injected vaccine (antigen or novel excipients) from the circulatory system.

5. **Require data from pharmacovigilance systems in the US and globally documenting a thorough investigation of serious adverse events, carried out by independent, impartial individuals. Rationale:**
    a. A major testament to the overall short-term safety of a medical product is the absence of serious adverse events (SAEs) when administered to millions. COVID-19 vaccines have now been administered to hundreds of millions of individuals, and it is vital that all reports of SAEs are thoroughly investigated to determine whether the vaccine played any role in the SAE.
    b. The most serious of all SAEs is death, and a CDC webpage on VAERS discusses 4,863 reports of death after COVID-19 vaccination reported between December 14, 2020 and May 24, 2021.[38] CDC states that:
        i. "CDC follows up on any report of death to request additional information to learn more about what occurred and to determine whether the death was a result of the vaccine or was unrelated."
        ii. "CDC and FDA physicians review each case report of death as soon as notified and CDC requests medical records to further assess reports."

iii. "A review of available clinical information, including death certificates, autopsy, and medical records has not established a causal link to COVID-19 vaccines."[38]

c. However, the FDA has stated that VAERS staff do not contact family members to learn more about the deaths. It stated: "Because the VAERS system is not designed to determine causality of adverse events, there is not a mechanism to follow-up with families for additional details. The determination of the cause of death is done by the certifying official who completes the death certificate or the pathologist who conducts the autopsy."[39]

d. Regulators in other countries have conducted detailed case investigations (e.g. Norway's investigation of 100 deaths amongst frail elderly following COVID-19 vaccination[40,41]).

e. FDA must require evidence of a thorough investigation into deaths and other SAEs—investigations that include contacting families to obtain a full medical history and personal accounts (in the case of deaths) and those who experienced the adverse event (in the case of other SAEs). Event adjudication, as done on data safety monitoring boards, must be in place in order to carry out detailed case investigations, and must be carried out by independent, impartial individuals.

6. **Clarify in revised Guidance that safety data from individuals receiving more than 2 vaccine doses must be submitted by vaccine manufacturers. Rationale:**

a. There is wide speculation that COVID-19 vaccines may become offered as annual vaccines, much like influenza vaccines, and regulators have already released guidance to this effect.[42]

b. Some manufacturers, such as Pfizer and Moderna, have indicated that a third dose may be necessary within the first 12 months. Other manufacturers may present similar claims in the future.[43]

c. The safety profile of multiple doses, possibly more than 70 doses across an average lifetime, must be considered at the time of licensure. Phase 3 trial data make clear that the safety profile differs by dose (e.g. dose 2 of the Pfizer and Moderna vaccines induce more severe systemic adverse events than dose 1).[44,45]

d. Information on the types and severity of adverse events that emerge following the administration of additional doses is necessary to better characterize long term safety.

7. **Ensure the inclusion of experts in gene therapy in the VRBPAC.** Rationale:

a. The COVID-19 vaccines produced by Pfizer, Moderna, and Janssen (as well as AstraZeneca, CanSinoBio (China) and Gamaleya Research Institute (Russia)) are gene based vaccines. Their mechanism of action differs substantially from all other vaccines that have been used on populations globally, as these novel vaccines work on the premise of gene delivery, and may therefore be considered a type of gene therapy. These gene based vaccines involve entering the cell, where the overwhelming majority of critical body activities occur, and utilizing

the host's cells to produce spike protein. This is an entirely different mechanism than that utilized by traditional vaccines such as inactivated, attenuated, subunit or protein-based (that are not intended to invade cells). Therefore, there is a need to consider safety with the informed perspectives of those with expertise in gene therapies.

8. **Ensure that the analysis of data and decisions regarding any COVID-19 vaccine BLA application are informed by experts with no financial or research relationships with any vaccine manufacturers within the last 36 months, both within FDA and amongst the composition of the VRBPAC. Rationale:**
    a. The public interest weighs strongly in favor of the evaluation of data and all decision making to be performed by competent individuals with independence from vaccine manufacturers (institutions that stand to gain or lose from a BLA decision on a COVID-19 vaccine). Disclosure requirements should be at least as stringent, if not more, than what is expected for writing a manuscript in a medical journal—namely, disclosure of relationships within the last 36 months, as requested by the International Committee of Medical Journal Editors (ICMJE). Insisting on this level of disclosure, and transparency of the disclosures, can publicly demonstrate the independence of the FDA's decision making process.[46]

Table 1a. Pfizer study report R-[?]-0072, biodistribution study submitted by Pfizer to Japanese regulator (PMDA).

2.6.5.5A. PHARMACOKINETICS: ORGAN DISTRIBUTION		**Test Article: modRNA encoding luciferase in LNP** **Report Number: R-[redacted]-0072**
Species (Strain):	Mice (BALB/c)	
Sex/Number of Animals:	Female/3 per group	
Feeding Condition:	Fed ad libitum	
Vehicle/Formulation:	Phosphate-buffered saline	
Method of Administration:	Intramuscular injection	
Dose (mg/kg):	1 µg/hind leg in gastrocnemius muscle (2 µg total)	
Number of Doses:	1	
Detection:	Bioluminescence measurement	
Sampling Time (hour):	6, 24, 48, 72 hours; 6 and 9 days post-injection	

Time point	**Total Mean Bioluminescence signal (photons/second)**		**Mean Bioluminescence signal in the liver (photons/second)**
	Buffer control	**modRNALuciferase in LNP**	**modRNALuciferase in LNP**
6 hours	1.28×10^{5}	1.26×10^{9}	4.94×10^{7}
24 hours	2.28×10^{5}	7.31×10^{8}	2.4×10^{6}
48 hours	1.40×10^{5}	2.10×10^{8}	Below detection[a]
72 hours	1.33×10^{5}	7.87×10^{7}	Below detection[a]
6 days	1.62×10^{5}	2.92×10^{6}	Below detection[a]
9 days	7.66×10^{4}	5.09×10^{5}	Below detection[a]

LNP = Lipid nanoparticle; modRNA = Nucleoside modified messenger RNA.
a. At or below the background level of the buffer control.

Source: Japan PMDA (PDF page 15).[37]

Table 1b. Pfizer study report 185350, biodistribution study submitted by Pfizer to Japanese regulator (PMDA).

2.6.5.5B. PHARMACOKINETICS: ORGAN DISTRIBUTION CONTINUED

Test Article: [^{3}H]-Labelled LNP-mRNA formulation containing ALC-0315 and ALC-0159
Report Number: 185350

Species (Strain):	Rat (Wistar Han)
Sex/Number of Animals:	Male and female/3 animals/sex/timepoint (21 animals/sex total for the 50 µg dose)
Feeding Condition:	Fed ad libitum
Method of Administration:	Intramuscular injection
Dose:	50 µg [^{3}H]-08-A01-C0 (lot # NC-0552-1)
Number of Doses:	1
Detection:	Radioactivity quantitation using liquid scintillation counting
Sampling Time (hour):	0.25, 1, 2, 4, 8, 24, and 48 hours post-injection

Sample	Mean total lipid concentration (µg lipid equivalent/g (or mL) (males and females combined)							% of administered dose (males and females combined)						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181	--	--	--	--	--	--	--
Adrenal glands	0.271	1.48	2.72	2.89	6.80	13.8	18.2	0.001	0.007	0.010	0.015	0.035	0.066	0.106
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365	0.000	0.001	0.001	0.001	0.001	0.002	0.002
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687	--	--	--	--	--	--	--
Bone marrow (femur)	0.479	0.960	1.24	1.24	1.84	2.49	3.77	--	--	--	--	--	--	--
Brain	0.045	0.100	0.138	0.115	0.073	0.069	0.068	0.007	0.013	0.020	0.016	0.011	0.010	0.009
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112	0.000	0.001	0.001	0.002	0.002	0.002	0.003
Heart	0.282	1.03	1.40	0.987	0.790	0.451	0.546	0.018	0.056	0.084	0.060	0.042	0.027	0.030
Injection site	128	394	311	338	213	195	165	19.9	52.6	31.6	28.4	21.9	29.1	24.6
Kidneys	0.391	1.16	2.05	0.924	0.590	0.426	0.425	0.050	0.124	0.211	0.109	0.075	0.054	0.057
Large intestine	0.013	0.048	0.093	0.287	0.649	1.10	1.34	0.008	0.025	0.065	0.192	0.405	0.692	0.762
Liver	0.737	4.63	11.0	16.5	26.5	19.2	24.3	0.602	2.87	7.33	11.9	18.1	15.4	16.2
Lung	0.492	1.21	1.83	1.50	1.15	1.04	1.09	0.052	0.101	0.178	0.169	0.122	0.101	0.101
Sample	**Total Lipid concentration (µg lipid equivalent/g [or mL]) (males and females combined)**							**% of Administered Dose (males and females combined)**						
	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h	0.25 h	1 h	2 h	4 h	8 h	24 h	48 h
Lymph node (mandibular)	0.064	0.189	0.290	0.408	0.534	0.554	0.727	--	--	--	--	--	--	--
Lymph node (mesenteric)	0.050	0.146	0.530	0.489	0.689	0.985	1.37	--	--	--	--	--	--	--
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192	--	--	--	--	--	--	--
Ovaries (females)	0.104	1.34	1.64	2.34	3.09	5.24	12.3	0.001	0.009	0.008	0.016	0.025	0.037	0.095
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599	0.003	0.007	0.014	0.015	0.015	0.011	0.019
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694	0.000	0.001	0.001	0.001	0.000	0.000	0.001
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170	0.001	0.001	0.002	0.003	0.003	0.004	0.003
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264	0.003	0.007	0.008	0.008	0.005	0.006	0.009
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253	--	--	--	--	--	--	--
Small intestine	0.030	0.221	0.476	0.879	1.28	1.30	1.47	0.024	0.130	0.319	0.543	0.776	0.906	0.835
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112	0.001	0.002	0.002	0.003	0.001	0.001	0.001
Spleen	0.334	2.47	7.73	10.3	22.1	20.1	23.4	0.013	0.093	0.325	0.385	0.982	0.821	1.03
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215	0.006	0.019	0.034	0.030	0.040	0.037	0.039
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320	0.007	0.010	0.017	0.030	0.034	0.074	0.074
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331	0.004	0.007	0.010	0.012	0.008	0.007	0.008
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.00	0.000	0.001	0.001	0.001	0.001	0.001	0.001
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456	0.002	0.011	0.015	0.008	0.016	0.018	0.022
Whole blood	1.97	4.37	5.40	3.05	1.31	0.909	0.420	--	--	--	--	--	--	--
Plasma	3.97	8.13	8.90	6.50	2.36	1.78	0.805	--	--	--	--	--	--	--
Blood:Plasma ratio[a]	0.815	0.515	0.550	0.510	0.555	0.530	0.540	--	--	--	--	--	--	--

Source: Japan PMDA (PDF page 16).[37]

Table 2. Modern study report 5002121, biodistribution study submitted by Moderna to Japanese regulator (PMDA).

表 2.6.4.4-3　雄性 Sprague Dawley ラットに mRNA-1647 100 µg を単回筋肉内接種したときの各組織における薬物動態パラメータ

Matrix	mRNA Construct	T_{max} (h)[a]	C_{max} (ng/mL)[a]	$AUC_{(0-t)}$ (ng × h/mL)[a,b]	$T_{1/2}$ (h)[a,c]	$AUC_{(0-t)}$ Ratio (Tissue/Plasma)[d]	$AUC_{(0-t)}$ Ratio (Tissue/Plasma) Average
Bone marrow	gB	NC	NC	NC	NC	NC	NR
	gH	8.0	0.254 ± 0.0871	7.85 ± 2.03	NC	0.316	
	gL	8.0	0.224 ± 0.0920	2.78 ± 1.03	NC	0.119	
	UL128	8.0	0.292 ± 0.120	3.53 ± 1.33	NC	0.147	
	UL130	NC	NC	NC	NC	NC	
	UL131A	8.0	0.186 ± 0.0829	2.05 ± 0.912	NC	0.0825	
Brain	gB	NC	NC	NC	NC	NC	NR
	gH	24.0	0.0800 ± 0.0491	2.19 ± 1.08	NC	0.0880	
	gL	2.0	0.0360 ± 0.0360	0.144 ± 0.144	NC	0.00615	
	UL128	2.0	0.0340 ± 0.0340	0.136 ± 0.136	NC	0.00564	
	UL130	NC	NC	NC	NC	NC	
	UL131A	NC	NC	NC	NC	NC	
Distal lymph node	gB	8.0	108 ± 101	1,460 ± 1,110	31.6	64.1	62.8
	gH	8.0	110 ± 102	1,490 ± 1,130	36.2	59.8	
	gL	8.0	117 ± 109	1,460 ± 1,200	30.6	62.6	
	UL128	8.0	125 ± 117	1,620 ± 1,290	32.1	67.1	
	UL130	8.0	129 ± 121	1,630 ± 1,330	27.9	64	
	UL131A	8.0	114 ± 108	1,470 ± 1,190	28.5	59.2	
Eye	gB	2.0	4.72 ± 2.77	26.7 ± 13.6	NC	1.18	1.24
	gH	2.0	3.92 ± 2.19	37.6 ± 11.0	NC	1.51	
	gL	2.0	3.23 ± 1.84	29.2 ± 9.75	NC	1.25	
	UL128	2.0	3.91 ± 2.19	34.5 ± 12.2	NC	1.43	
	UL130	2.0	3.61 ± 2.14	21.3 ± 11.0	NC	0.838	
	UL131A	2.0	3.43 ± 1.96	31.1 ± 10.2	NC	1.26	
Heart	gB	NC	NC	NC	NC	NC	NR
	gH	8.0	0.548 ± 0.107	9.94 ± 1.85	NC	0.400	
	gL	8.0	0.220 ± 0.0907	2.96 ± 1.05	NC	0.127	
	UL128	8.0	0.276 ± 0.113	4.49 ± 1.51	NC	0.186	
	UL130	NC	NC	NC	NC	NC	
	UL131A	8.0	0.312 ± 0.0896	3.71 ± 1.02	NC	0.150	
Injection site, muscle	gB	2.0	1,770 ± 803	27,100 ± 4,880	13.5	1190	939
	gH	2.0	1,720 ± 828	26,100 ± 4,700	17.1	1050	
	gL	2.0	1,310 ± 638	20,900 ± 3,720	15.2	893	
	UL128	2.0	1,620 ± 720	25,300 ± 4,090	14.9	1050	
	UL130	2.0	1,630 ± 777	24,500 ± 4,240	13.8	961	
	UL131A	8.0	427 ± 210	12,100 ± 2,830	15.0	487	
Jejunum	gB	NC	NC	NC	NC	NC	NR
	gH	8.0	0.0800 ± 0.0490	2.06 ± 1.04	NC	0.0827	
	gL	2.0	0.0700 ± 0.0429	0.720 ± 0.472	NC	0.0308	
	UL128	NC	NC	NC	NC	NC	
	UL130	NC	NC	NC	NC	NC	
	UL131A	NC	NC	NC	NC	NC	
Kidney	gB	NC	NC	NC	NC	NC	NR
	gH	NC	NC	NC	NC	NC	
	gL	NC	NC	NC	NC	NC	
	UL128	NC	NC	NC	NC	NC	
	UL130	NC	NC	NC	NC	NC	
	UL131A	NC	NC	NC	NC	NC	
Liver	gB	2.0	2.16 ± 1.21	8.65 ± 4.83	NC	0.381	0.499
	gH	2.0	2.12 ± 0.982	16.8 ± 4.15	NC	0.674	
	gL	2.0	1.30 ± 0.432	11.0 ± 2.37	NC	0.470	
	UL128	2.0	2.00 ± 0.814	13.7 ± 3.72	NC	0.570	
	UL130	2.0	1.87 ± 1.01	7.46 ± 4.04	NC	0.293	
	UL131A	2.0	1.99 ± 0.928	13.9 ± 4.04	NC	0.562	
Lung	gB	NC	NC	NC	NC	NC	NR
	gH	8.0	0.442 ± 0.130	8.04 ± 1.96	NC	0.323	
	gL	8.0	0.274 ± 0.0984	3.45 ± 1.12	NC	0.148	
	UL128	8.0	0.340 ± 0.129	5.40 ± 1.74	NC	0.224	
	UL130	8.0	0.188 ± 0.188	2.07 ± 2.07	NC	0.0812	
	UL131A	8.0	0.310 ± 0.111	4.86 ± 1.49	NC	0.196	

Proximal lymph nodes	gB	2.0	260 ± 121	5,850 ± 949	33.5	257	201
	gH	8.0	206 ± 51.6	4,860 ± 722	38.2	195	
	gL	2.0	175 ± 81.9	3,460 ± 538	36.3	148	
	UL128	8.0	246 ± 66.6	5,190 ± 875	32.8	215	
	UL130	8.0	252 ± 67.2	5,240 ± 881	35.7	206	
	UL131A	2.0	225 ± 106	4,600 ± 719	32.2	185	
Spleen	gB	2.0	7.36 ± 3.81	460 ± 52.9	46.9	20.2	13.4
	gH	24.0	5.63 ± 1.28	371 ± 39.5	83.0	14.9	
	gL	8.0	3.83 ± 1.04	196 ± 21.0	68.2	8.36	
	UL128	24.0	4.87 ± 1.22	297 ± 34.8	68.8	12.3	
	UL130	8.0	5.03 ± 1.41	288 ± 33.0	64.9	11.3	
	UL131A	2.0	5.10 ± 2.64	277 ± 33.1	46.2	11.2	
Stomach	gB	NC	NC	NC	NC	NC	NR
	gH	8.0	0.110 ± 0.0696	3.49 ± 1.59	NC	0.140	
	gL	8.0	0.0800 ± 0.0499	2.07 ± 1.19	NC	0.0886	
	UL128	24.0	0.102 ± 0.0648	2.85 ± 1.47	NC	0.118	
	UL130	NC	NC	NC	NC	NC	
	UL131A	24.0	0.0980 ± 0.0634	2.53 ± 1.39	NC	0.102	
Testes	gB	2.0	1.16 ± 0.719	4.64 ± 2.88	NC	0.204	0.209
	gH	2.0	1.11 ± 0.480	5.52 ± 2.20	NC	0.222	
	gL	8.0	0.420 ± 0.335	6.08 ± 3.73	NC	0.260	
	UL128	2.0	0.946 ± 0.397	4.73 ± 1.85	NC	0.196	
	UL130	2.0	0.682 ± 0.442	2.73 ± 1.77	NC	0.107	
	UL131A	2.0	0.872 ± 0.380	4.54 ± 1.85	NC	0.183	

Abbreviations: gB = glycoprotein B; gH = glycoprotein H; gL = glycoprotein L; IM = intramuscular; NC = not calculable (insufficient data points above the lower limit of quantitation); NR = not reported (some constructs measured all samples as below limit of quantitation).

[a] T_{max} and $T_{1/2}$ data reported as the mean; C_{max} and $AUC_{(0-t)}$ data reported as the mean ± standard error.

[b] For the bone marrow, brain, jejunum, heart, liver, lung, stomach, and testes, $AUC_{(0-t)}$ was calculated using less than 3 quantifiable mean concentrations and therefore is an estimate.

[c] Due to the lack of a distinct elimination phase in plasma, the $T_{1/2}$ of the mRNA constructs could not be calculated; however, the $T_{1/2}$ was estimated to range from 2.7 to 3.8 hours.

[d] For $AUC_{(0-t)}$ Ratio, samples listed as NC were not calculable because all samples were below limit of quantitation.

Source: Report 5002121 Amendment 1 (Appendix 8, Table 2 and Table 3)

Source: Japan PMDA (PDF page 7).[47]

III. ENVIRONMENT IMPACT

The petitioner hereby states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. Sections 25.30 and 25.31.

IV. ECONOMIC IMPACT

Economic impact information will be submitted upon request of the commissioner.

V. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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Marks Decl. Exhibit G

August 23, 2021

Linda Wastila, BSPharm, MSPH, PhD
Representative
Coalition Advocating for Adequately Licensed Medicines (CAALM)

Re: Citizen Petition (Docket Number FDA-2021-P-0786)

Dear Petitioner,

This letter responds to the citizen petition that the Coalition Advocating for Adequately Licensed Medicines (CAALM) (the Petitioner, you) submitted to the Food and Drug Administration (FDA, the Agency, we) relating to licensure of vaccines to prevent Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (the CP).

In the CP, Petitioner requests that FDA:

1. "Confirm, in revised Guidance, that the FDA expects a minimum of 2 years of follow-up of participants enrolled in pivotal clinical trials, even if trials are unblinded and lack a placebo control";
2. "Require data demonstrating substantial evidence of clinical effectiveness that outweighs harms, in all special populations, as a condition of consideration of including these populations among the indicated populations" including the special populations "infants, children, and adolescents; those with past SARS-CoV-2 infection; immunosuppressed individuals; those with history of or current cancer; individuals with hematological disorders or autoimmune diseases; pregnant or nursing women; and frail older adults";
3. "Require data on the safety and pharmacokinetic profiles of the spike protein";
4. "Require data from biodistribution studies investigating the actual COVID-19 vaccines";
5. "Require data from pharmacovigilance systems in the US and globally documenting a thorough investigation of serious adverse events, carried out by independent, impartial individuals";
6. "Clarify in revised Guidance that safety data from individuals receiving more than 2 vaccine doses must be submitted";
7. "Ensure the inclusion of experts in gene therapy in the VRBPAC"; and
8. "Ensure that the analysis of data and decisions regarding any COVID-19 vaccine BLA application are informed by experts with no financial or research relationships with any vaccine manufacturers within the last 36 months, both within FDA and amongst the composition of the VRBPAC."

CP at 3-4.

U.S. Food and Drug Administration
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This letter responds to the CP in full. FDA has carefully reviewed the CP and other relevant information available to the Agency. Based on our review of these materials and for the reasons described below, we conclude that the CP does not contain facts demonstrating any reasonable grounds for the requested action. In accordance with 21 CFR § 10.30(e)(3), and for the reasons stated below, FDA is denying the CP.

In this letter, we discuss the requirements for licensed vaccines. We then turn to the requests contained in the CP. We consider each of your requests in light of the legal standards for FDA action, and provide our conclusions based on the facts, the science, and the law.

I. Background

There is currently a pandemic of respiratory disease, COVID-19, caused by a novel coronavirus, SARS-CoV-2. The COVID-19 pandemic presents an extraordinary challenge to global health. On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19.[1] On February 4, 2020, pursuant to section 564 of the FD&C Act, the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves the virus that causes COVID-19.[2] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic ("COVID-19 EUA Declaration"), pursuant to section 564(b)(1) of the FD&C Act.[3] In addition, on March 13, 2020, the Presidential declared a national emergency in response to COVID-19.[4]

Commercial vaccine manufacturers and other entities are developing COVID-19 vaccine candidates, and clinical studies of these vaccines are underway and/or have been completed. Between December 11, 2020 and February 27, 2021, FDA issued emergency use authorizations for three vaccines to prevent COVID-19, including vaccines sponsored by Pfizer Inc. (Pfizer); ModernaTX, Inc. (Moderna); and Janssen Biotech, Inc. (Janssen), a pharmaceutical company of Johnson & Johnson. FDA received a Biologics License Application (BLA) for the COVID-19 vaccine, BNT162b2, intended to prevent COVID-19 in individuals 16 years of age and older. As announced by FDA on August 23, 2021, the Agency is issuing a biologics license

[1] Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists (Originally issued Jan. 31, 2020, and subsequently renewed), https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.
[2] HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[3] HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.
[4] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak, issued March 13, 2020, https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.

for this COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) to BioNTech Manufacturing GmbH.[5,6]

II. Vaccines That Are FDA-Licensed Meet Relevant Statutory Requirements

1. Vaccines Are Shown to Be Safe, Pure, and Potent at the Time of Licensure

FDA has a stringent regulatory process for licensing vaccines.[7,8] The Public Health Service Act (PHS Act) authorizes FDA to license biological products, including vaccines, if they have been demonstrated to be "safe, pure, and potent."[9] Prior to approval by FDA, vaccines are extensively tested in non-clinical studies and in humans. FDA's regulations describe some of the extensive data and information that each sponsor of a vaccine must submit to FDA in order to demonstrate the product's safety before FDA will consider licensing the vaccine. FDA requires that the sponsor's BLA include, among other things, data derived from nonclinical and clinical studies showing the product's safety, purity, and potency; a full description of manufacturing methods for the product; data establishing the product's stability through the dating period; and a representative sample of the product and summaries of results of tests performed on the lot(s) represented by the sample.[10]

As is evident from the language of the PHS Act and FDA's regulations, the licensure process for a vaccine requires the sponsor to establish, through carefully controlled laboratory and clinical studies, as well as through other data, that the product is safe and effective for its approved indication(s) and use. FDA's multidisciplinary review teams then rigorously evaluate the sponsor's laboratory and clinical data, as well as other information, to help assess whether the safety, purity, and potency of a vaccine has been demonstrated.[11] Only when FDA's standards are met is a vaccine licensed.

FDA regulations explicitly state that "[a]pproval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products."[12] Therefore, the manufacturers of vaccines that have been licensed in the U.S. have necessarily demonstrated the safety of the vaccines within the meaning of the applicable statutory and regulatory provisions before the vaccines were licensed and allowed to be marketed.

For more information on FDA's thorough process for evaluating the safety of vaccines, see Appendix I of this letter, *Aspects of Vaccine Development and Process for Licensure*.

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[5] BioNTech Manufacturing GmbH is the biologics license holder for this vaccine, which is manufactured by Pfizer Inc. for BioNTech Manufacturing GmbH (hereinafter "BioNTech").
[6] The basis for FDA's licensure decision is set forth in FDA's Summary Basis for Regulatory Action for the BioNTech application. This memorandum will be posted on fda.gov. We incorporate by reference the SBRA for the BLA.
[7] CDC, Ensuring the Safety of Vaccines in the United States, February 2013, https://www.cdc.gov/vaccines/hcp/patient-ed/conversations/downloads/vacsafe-ensuring-bw-office.pdf.
[8] Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[9] 42 U.S.C. § 262(a)(2)(C)(i)(I).
[10] 21 CFR § 601.2(a).
[11] Vaccines, last updated January 2021, https://www.fda.gov/vaccines-blood-biologics/vaccines.
[12] 21 CFR § 601.2(d) (emphasis added).

2. Vaccine Safety Continues to Be Monitored Post-Licensure

FDA's oversight of vaccine safety continues after licensure of the product. Once the licensed vaccine is on the market, post-marketing surveillance of vaccine safety is conducted in order to detect any rare, serious, or unexpected adverse events, as well as to monitor vaccine lots. FDA employs multiple surveillance systems and databases to continue to evaluate the safety of these vaccines. In certain cases, FDA may require the manufacturer to conduct post-marketing studies to further assess known or potential serious risks.

For more information on post-licensure safety monitoring of vaccines, see Appendix II of this letter, *Aspects of Vaccine Postmarketing Safety Monitoring*.

III. Discussion

The CP makes a series of requests regarding the data to be submitted in support of licensure of vaccines to prevent COVID-19. Much of the key data supporting licensure applications is developed during the clinical trial process, which is subject to FDA's investigational new drug process.[13]

A. Investigational New Drugs

Before a vaccine is licensed (approved) by FDA for use by the public, FDA requires that it undergo a rigorous and extensive development program to determine the vaccine's safety and effectiveness. This development program encompasses preclinical research (laboratory research, animal studies[14]) and clinical studies. At the preclinical stage, the sponsor focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies. Clinical studies, in humans, are conducted under well-defined conditions and with careful safety monitoring through all the phases of the investigational new drug process. FDA's regulations governing the conduct of clinical investigations are set out at 21 CFR Part 312.

Before conducting a clinical investigation in the U.S. in which a new drug or biological product is administered to humans, a sponsor must submit an investigational new drug application (IND) to FDA.[15] The IND describes the proposed clinical study in detail and, among other things, helps protect the safety and rights of human subjects.[16] In addition to other information, an IND must contain information on clinical protocols and clinical investigators. Detailed protocols for proposed clinical studies permit FDA to assess whether the initial-phase trials will expose subjects to unnecessary risks. Information on the qualifications of clinical investigators (professionals, generally physicians, who oversee the administration of the experimental drug) permits FDA to assess whether they are qualified to fulfill their clinical trial duties. The IND

[13] See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).

[14] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[15] See 21 CFR § 312.20(a).

[16] For additional information regarding the IND review process and general responsibilities of sponsor-investigators related to clinical investigations see Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators; Draft Guidance for Industry, May 2015, https://www.fda.gov/media/92604/download.

includes commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB),[17] and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials, unless FDA informs the sponsor that the trial may begin earlier. During this time, FDA reviews the IND. FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and Phase 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.[18]

FDA's regulations provide that, once an IND is in effect, the sponsor may conduct a clinical investigation of the product, with the investigation generally being divided into three phases. With respect to vaccines, the initial human studies, referred to as Phase 1 studies, are generally safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase 2 studies may include up to several hundred individuals and are designed to provide information regarding the incidence of common short-term side effects such as redness and swelling at the injection site or fever and to further describe the immune response to the investigational vaccine. If an investigational new vaccine progresses past Phase 1 and Phase 2 studies, it may progress to Phase 3 studies. For Phase 3 studies, the sample size is often determined by the number of subjects required to establish the effectiveness of the new vaccine, which may be in the thousands or tens of thousands of subjects. Phase 3 studies provide the critical documentation of effectiveness and important additional safety data required for licensing.

At any stage of development, if data raise significant concerns about either safety or effectiveness, FDA may request additional information or studies; FDA may also halt ongoing clinical studies. The FD&C Act provides a specific mechanism, called a "clinical hold," for prohibiting sponsors of clinical investigations from conducting the investigation (section 505(i)(3) of the FD&C Act; 21 U.S.C. § 355(i)(3)), and FDA's IND regulations in 21 CFR § 312.42 identify the circumstances that may justify a clinical hold. Generally, a clinical hold is an order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or to suspend an ongoing investigation.[19]

B. The Citizen Petition

In the CP, Petitioner requests that before FDA licenses any vaccine[20] for COVID-19, the agency require certain data be submitted. Because much of the relevant data is the kind that would be

[17] The IRB is a panel of scientists and non-scientists in hospitals and research institutions that oversees clinical research. IRBs approve clinical study protocols, which describe the type of people who may participate in the clinical study; the schedule of tests and procedures; the medications and dosages to be studied; the length of the study; the study's objectives; and other details. IRBs make sure that the study is acceptable, that participants have given consent and are fully informed of the risks, and that researchers take appropriate steps to protect patients from harm. See The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective web page, last updated November 2017, https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.

[18] 21 CFR § 312.22(a).

[19] 21 CFR § 312.42(a).

[20] The CP refers to "granting" a license. See, e.g., CP at 1. FDA generally refers to *issuing* licenses, or *approving* a BLA. See 21 CFR § 601.2(d); 21 CFR § 601.4(a).

gathered during clinical trials, we interpret the CP as asking that FDA require the sponsors to make the requested changes to their investigations, as well as, in some cases, to submit certain other data. As explained above, with certain exceptions, clinical investigations in which a drug is administered to human subjects must be conducted under an IND submitted to FDA by the sponsor. FDA's review of an IND includes a review of the study protocol which describes, among other things, the design of the clinical study, including the identified endpoints and methods for assessing the safety and effectiveness of the investigational product.

Below, we discuss the requested changes to the study design and other data submissions.

1. Petitioner's request to require data demonstrating "substantial evidence of clinical effectiveness that outweighs harms" in all "special populations"

Petitioner asks that, prior to issuing a license for a COVID-19 vaccine, FDA require certain types of *clinical* data, specifically:

> data demonstrating substantial evidence of clinical effectiveness that outweighs harms, in all special populations, as a condition of consideration of including these populations among the indicated populations. Special populations include: infants, children, and adolescents; those with past SARS-CoV-2 infection; immunosuppressed individuals; those with history of or current cancer; individuals with hematological disorders or autoimmune diseases; pregnant or nursing women; and frail older adults.

CP at 3.

Petitioner refers to the ongoing phase 3 trials of COVID-19 vaccines for the Moderna, Pfizer, and Janssen products, and states that the trials "largely (or wholly) excluded" certain identified populations. CP at 5. Petitioner states that there should be information about "what kind of efficacy" exists for these populations, and refers to "reduction in risk of symptomatic COVID-19 vs. reduction in risk of hospitalization or death." CP at 6.

Thus, Petitioner appears to request that FDA require evidence derived from clinical trials to provide evidence of effectiveness for each of the identified populations, and also that clinical trials be designed and conducted in each population to assess the effectiveness of these vaccines to prevent COVID-19 disease of varying severity in the specified populations.

In support of Petitioner's request, Petitioner asserts that "efficacy and safety of medicines often differs amongst populations" and that the risks of SARS-CoV-2 infection are "considerably lower in infants, children, and adolescents in comparison to adults." CP at 5.

FDA addressed trial populations in the guidance.[21] In the June 2020 guidance, FDA noted that while certain exclusions were recommended, for example "[e]xclusion of participants at higher risk of severe COVID-19 from early phase studies" in order "to mitigate potential risk of vaccine associated [enhanced respiratory disease] until additional data to inform that potential risk becomes available through ongoing product development,"[22] FDA in general "encourages the

[21] Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry, June 2020 (June 2020 Guidance), https://www.fda.gov/media/139638/download.
[22] June 2020 Guidance at 10.

inclusion of diverse populations in all phases of vaccine clinical development."[23] FDA also noted in the June 2020 Guidance that "vaccine safety and COVID-19 outcomes in individuals with prior SARS-CoV-2 infection, which might have been asymptomatic, is also important to examine because pre-vaccination screening for prior infection is unlikely to occur in practice with the deployment of licensed COVID-19 vaccines."[24]

With respect to the pediatric population, the June 2020 Guidance acknowledged that "the safety and effectiveness of COVID-19 vaccines, may be different in children compared with adults"[25] and recommended that "considerations on the prospect of direct benefit and acceptable risk to support initiation of pediatric studies, and the appropriate design and endpoints for pediatric studies, should be discussed in the context of specific vaccine development programs."[26]

Although the June 2020 Guidance includes various recommendations, ultimately FDA licensure decisions are based on an evaluation of the entirety of the data contained in a BLA and a finding that a vaccine's benefits outweigh its potential risks.

In assessing benefits and risks, FDA takes into account a number of factors including, but not limited to, the evidence for benefit, the requested indication, severity of the disease or condition, treatment alternatives, and the type and severity of adverse events. In general, the evidence for benefit is based on the results of clinical trials. In some cases, vaccine clinical trials assess clinical disease endpoints. In other cases, it may be scientifically acceptable to utilize immunogenicity endpoints.

In assessing benefits for particular populations, FDA is not limited to considering evidence of effectiveness based on clinical trial studies with disease endpoints. In some cases, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults.[27] Furthermore, a study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group.[28] There are times where it is scientifically appropriate to demonstrate effectiveness using scientifically accepted immune marker(s) of protection or to infer effectiveness for a population through immunobridging.

In assessing risks, FDA takes into account the type, frequency, and severity of any adverse events.

The benefit-risk assessment will be informed by the body of evidence about the vaccine's safety and effectiveness submitted by an applicant in the BLA, the severity of the target disease, and the target population. Thus, in approving or authorizing a vaccine for use in a particular population (such as children), FDA will take into account the severity of the disease in the population as well as the benefits of the vaccine.

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[23] Id. at 11.
[24] Id.
[25] Id.
[26] Id.
[27] See section 505B(a)(2)(B)(i) of the FD&C Act (21 U.S.C. 355c(a)(2)(B)(i)) (providing that "[i]f the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies").
[28] See section 505B(a)(2)(B)(ii) of the FD&C Act (21 U.S.C. 355c(a)(2)(B)(ii)) (providing that "[a] study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group").

To require the Petitioner's proposed across-the-board approach—i.e., of requiring effectiveness data from clinical trials specific to each population group and specifically designed to evaluate disease endpoints of varying severity (e.g., hospitalization and death) in all of the specified populations—would not reflect the scientifically valid methods of assessing safety and effectiveness described above. Petitioner has not provided a scientific justification for why such tools as immunobridging or extrapolation across population groups cannot be used. Therefore, we deny Petitioner's request[29] to require effectiveness data from clinical trials specifically designed to assess disease endpoints of varying severity (e.g., hospitalization and death) for each of the identified populations as a condition of licensing a COVID-19 vaccine.[30,31]

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[29] In denying Petitioner's request, we do not dispute Petitioner's statement that the risks of SARS-CoV-2 infection can differ across population groups. That has been a feature of the pandemic's effects thus far, with children and adolescents generally experiencing a milder disease course compared to older adults. But as with adults, children and adolescents with underlying conditions such as asthma, chronic lung disease, and cancer are at higher risk than their healthier counterparts for COVID-19-related hospitalization and death. See generally Emergency Use Authorization (EUA) Amendment for an Unapproved Product Review Memorandum (pertaining to FDA's authorization of the Pfizer-BioNTech COVID-19 Vaccine for individuals 12 years and older), https://www.fda.gov/media/148542/download. These are features of COVID-19 that FDA may consider in weighing the risks and benefits of COVID-19 vaccines for different populations.

[30] With respect to Petitioner's statement that it is important to consider "how much efficacy exists" (CP at 6) for different populations, with the example of reduction of risk of hospitalization or death vs. reduction of risk of symptomatic COVID-19, we agree that severity of disease experienced by different groups is an important consideration that may be accounted for in a risk-benefit analysis. What we disagree with is Petitioner's apparent request that FDA only accept the results of clinical trials that have different endpoints for different populations (e.g., hospitalization or death for a younger population and symptomatic COVID-19 for older populations). A clinical trial endpoint of symptomatic disease for all populations included in the trial may provide sufficient information for FDA to adequately assess the risks and benefits of the vaccine, and FDA may evaluate the effectiveness of the vaccine in different populations by considering subgroup analyses of the data including analyses of vaccine effectiveness against disease of varying severity using pre-specified case definitions.

[31] With respect to Petitioner's statement that individuals with past SARS-CoV-2 infection "are likely to have immunity to subsequent infections for as long or longer than immunity conferred by vaccine," and that they "may also be at heightened risk for adverse effects," (CP at 5) we note that there is scientific uncertainty about the duration of protection provided by previous natural infection, but that the scientific community believes that vaccines may provide a longer duration of protection than that provided by natural infection. See CDC, COVID-19 Frequently Asked Questions, last updated August 2021, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html; Boyton, R. and D Altmann, 2021, Risk of SARS-CoV-2 reinfection after natural infection, Lancet, 397(10280):1161-1163, https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00662-0/fulltext

In addition, you state that individuals with previous infection "may also be at heightened risk for adverse effects." CP at 5. The sources that you cite for this proposition are unavailing. First, the Krammer et al. publication (http://medrxiv.org/lookup/doi/10.1101/2021.01.29.21250653) does not assert safety problems with this population receiving COVID-19 vaccines; rather, the publication asserts that these individuals could receive only one dose of vaccine without negatively impacting their antibody titers and sparing them from unnecessary local and systemic adverse reactions (e.g., pain, swelling, fatigue, headache, chills, fever, muscle or joint pains) while also freeing up many urgently needed vaccine doses. The Samanovic et al. publication (http://dx.doi.org/10.1101/2021.02.07.21251311) similarly does not identify safety concerns, but rather concludes that prior history of COVID-19 affects adaptive immune responses to mRNA vaccination. The Camara et al. publication (https://www.biorxiv.org/content/10.1101/2021.03.22.436441v1) asserts only that the second dose may not be necessary in individuals with prior infection and that a second dose may cause a "possible contraction of their spike-specific memory T cell immunity," while also noting that "[o]ur study has clear limitations" and that "more detailed analysis of the phenotype of the spike-specific T cells induced by COVID-19 vaccines both in naïve and

2. Petitioner's request to require data on the safety and pharmacokinetic profiles of the spike protein

Petitioner asks FDA to "[r]equire data on the safety and pharmacokinetic profiles of the spike protein" prior to licensing any COVID-19 vaccine. CP at 6. In support of this request, Petitioner states that "[i]n-situ production of SARS-CoV-2 spike protein is the target mechanism of action of all COVID-19 vaccines with an EUA at present. Therefore, the safety profile of the spike protein itself (i.e., in the absence of virus) must be thoroughly understood in the range of populations on the indications list." CP at 6.

This request relates to the technology used to make the COVID-19 vaccines that have been authorized by FDA for emergency use. The Pfizer-BioNTech and Moderna vaccines contain a piece of mRNA that instructs cells in the body to make the distinctive "spike" protein of the SARS-COV-2 virus. The Janssen COVID-19 vaccine is manufactured using a specific type of virus called adenovirus type 26 (Ad26) that delivers a piece of the DNA that is used to make the distinctive "spike" protein of the SARS-CoV-2 virus.

Your request appears to be premised on the notion that licensure should be contingent on sponsors' conducting safety studies of a specific protein produced by the COVID-19 vaccines that is designed to elicit an immune response. Contrary to the assumption underlying your request, it is not scientifically necessary to require toxicological or pharmacokinetic studies in individuals to evaluate specific features of a vaccine outside the context of evaluating the vaccine as a whole. In making a licensure decision, FDA determines whether the data and information provided by a manufacturer have demonstrated that a vaccine is safe, pure, and potent. In making a determination about the safety of a vaccine, the agency evaluates the complete manufacturing process and whether specific features of a vaccine are such that the finished product itself, when used at the recommended dose, is safe for the recipient. FDA applies its

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recovered individuals are needed to answer these questions." Petitioner also references a preprint by Levi et al. (https://www.medrxiv.org/content/10.1101/2021.02.01.21250923v2). In the published version of that study, the authors conclude that "[o]ne vaccine dose is sufficient in symptomatic SARS-CoV-2-exposed subjects to reach a high titer of antibodies, suggesting no need for a second dose, particularly in light of current [sic] vaccine shortage." Levi et al. One Dose of SARS-CoV-2 Vaccine Exponentially Increases Antibodies in Individuals Who Have Recovered from Symptomatic COVID-19, J Clin Invest. 2021;131(12):e149154: https://www.jci.org/articles/view/149154). Levi et al. does not identify safety concerns with COVID-19 vaccines.

We note that history of infection prior to vaccination is not usually known in adverse event reports (either because it wasn't reported, or because it could have been asymptomatic and the patient never knew they had infection). Likewise, there could be a reporting bias for a reporting system like VAERS, which relies on vaccine recipients, healthcare providers, or others to initiate reports to the system, because individuals who were infected previously might be more likely to report adverse events. However, FDA, together with CDC, has not become aware of data from VAERS to suggest an increased frequency of adverse events in vaccinees who were infected with SARS-CoV-2 prior to vaccination. FDA and CDC Medical Officers conduct on-going review of certain, serious adverse events of special interest for the COVID vaccines. These reviews often include examination of the narrative and other fields which would contain information about past infection, if provided. Additionally, CDC and the VAERS Program contractor collect follow-up medical records for certain serious reports. Teams of physicians, nurses, and other reviewers abstract key clinical details, including medical history, from these records. The reviewers conducting these on-going surveillance efforts have not identified patterns of adverse events associated with prior infection.

sound scientific judgment in evaluating vaccines and other biological products, and ensures that vaccines licensed by the agency are safe within the meaning of the PHSA, the FD&C Act, and implementing regulations.

With respect to the spike protein feature of vaccines for COVID-19, while there have been numerous claims on social media suggesting that the spike protein is toxic,[32] there are in fact no reliable scientific data to indicate that the spike protein is toxic or that it lingers at any toxic level in the body after vaccination. Below, we list the publications you cite in footnotes 15-28 of your petition in support of what you describe as "safety concerns" with the spike protein feature of authorized vaccines.[33] The left column identifies the relevant footnote in your petition and the accompanying citation, and the right column describes FDA's analysis of the publication. The information in the right column explains why you have not in fact presented data showing safety problems with the spike protein feature of vaccines that would cause the vaccines to be unsafe.

Publication cited by Petitioner in support of "safety concerns" regarding spike protein	**FDA analysis**
Footnote 15: Ogata AF, Cheng C-A, Desjardins M, Senussi Y, Sherman AC, Powell M, et al. Circulating SARS-CoV-2 Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients. Clin Infect Dis [Internet]. 2021 May 20; Available from: http://dx.doi.org/10.1093/cid/ciab465	This work conducted in a small number of individuals (n=13) documents that shortly following administration of the mRNA-1273 COVID-19 vaccine, SAR-CoV-2 spike protein was detectible in the plasma of 11 of the 13. Clearance of the protein from the circulation was associated with the development of IgG and IgA antibodies. The authors suggest a mechanism that might have led to the findings, based on the immune response to the vaccine. This paper documents the appearance of spike protein in plasma and its clearance with development of an immune response. This publication does not provide evidence that authorized COVID-19 vaccines are unsafe.
Footnote 16: Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med [Internet]. 2005 Aug;11(8):875–9. Available from: http://dx.doi.org/10.1038/nm1267	This article relates to SARS-CoV, the causative agent of SARS, an atypical pneumonia that occurred in several countries in 2002-2003. It was published in 2005 before the discovery of SARS-CoV-2 and the development of vaccines to prevent COVID-19. Therefore, the reports in this publication do not present safety concerns about the use of the spike protein in vaccines.
Footnote 17: Chen I-Y, Chang SC, Wu H-Y, Yu T-C, Wei W-C, Lin S, et al. Upregulation of the chemokine (C-C motif) ligand 2 via a severe acute respiratory syndrome coronavirus spike-ACE2 signaling pathway. J	This 2010 publication describes in vitro studies with SARS-CoV. It was published in 2010 before the discovery of SARS-CoV-2 and the development of vaccines to prevent COVID-19. The publication therefore does not present any evidence of safety

[32] See, e.g., FactCheck.org, COVID-19 Vaccine-Generated Spike Protein is Safe, Contrary to Viral Claims, https://www.factcheck.org/2021/07/scicheck-covid-19-vaccine-generated-spike-protein-is-safe-contrary-to-viral-claims/ (describing spread of social media claims about the spike protein); Lin, R., 2021, Busted: 3 dangerous social-media myths about COVID-19 vaccines, LA Times, https://www.latimes.com/california/story/2021-06-03/covid-19-vaccine-myths-busted (same); Dupuy, B., 2021, Spike protein produced by vaccine not toxic, AP, https://apnews.com/article/fact-checking-377989296609 (same).

[33] See Sec. 3(b) of the CP, which refers to footnotes 15-28 as support for asserted safety concerns with the spike protein.

Virol [Internet]. 2010 Aug;84(15):7703–12. Available from: http://dx.doi.org/10.1128/JVI.02560-09	concerns related to the formulation of COVID-19 vaccines.
Footnote 18: Patra T, Meyer K, Geerling L, Isbell TS, Hoft DF, Brien J, et al. SARS-CoV-2 spike protein promotes IL6 trans-signaling by activation of angiotensin II receptor signaling in epithelial cells. PLoS Pathog [Internet]. 2020 Dec;16(12):e1009128. Available from: http://dx.doi.org/10.1371/journal.ppat.1009128	This publication pertains to SARS-CoV-2 infection and disease progression, but does not relate to vaccines to prevent COVID-19. The publication therefore does not present any evidence of safety concerns related to the formulation of COVID-19 vaccines.
Footnote 19: Zhang S, Liu Y, Wang X, Yang L, Li H, Wang Y, et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol [Internet]. 2020 Sep 4;13(1):120. Available from: http://dx.doi.org/10.1186/s13045-020-00954-7	This publication pertains to SARS-CoV-2 infection and disease progression, but does not relate to vaccines to prevent COVID-19. The publication therefore does not present any evidence of safety concerns related to the formulation of COVID-19 vaccines.
Footnote 20: Suresh SJ, Suzuki YJ. SARS-CoV-2 Spike Protein and Lung Vascular Cells. Journal of Respiration [Internet]. 2020 Dec 31 [cited 2021 May 25];1(1):40–8. Available from: https://www.mdpi.com/2673-527X/1/1/4	This publication states that "it is critical to understand the biological effects of this [spike] protein on human cells to ensure that it does not promote long-term adverse health consequences" and that "[f]urther work is needed to understand the effects of various SARS-CoV-2 spike protein segments" used in vaccines. But the publication does not in fact report any adverse effects of authorized vaccines. Nor does it conclude that use of spike protein in authorized vaccines causes the vaccines to be unsafe.
Footnote 21: Angeli F, Spanevello A, Reboldi G, Visca D, Verdecchia P. SARS-CoV-2 vaccines: Lights and shadows. Eur J Intern Med [Internet]. 2021 Apr 30; Available from: http://dx.doi.org/10.1016/j.ejim.2021.04.019	This article summarizes the features of several COVID-19 vaccines and discusses potential interactions between the spike protein of vaccines with the cardiovascular system. The article notes "[t]he basic mechanisms …require further research…" and that newer vaccines might be developed; however, it does not state that the spike protein itself should be studied in people.
Footnote 22: Han M, Pandey D. ZMPSTE24 Regulates SARS-CoV-2 Spike Protein-enhanced Expression of Endothelial Plasminogen Activator Inhibitor-1. Am J Respir Cell Mol Biol [Internet]. 2021 May 18; Available from: http://dx.doi.org/10.1165/rcmb.2020-0544OC	This publication pertains to COVID-19 disease, but does not relate to vaccines to prevent COVID-19. The publication therefore does not present any evidence of safety concerns related to the formulation of COVID-19 vaccines.
Footnote 23: Rhea EM, Logsdon AF, Hansen KM, Williams LM, Reed MJ, Baumann KK, et al. The S1 protein of SARS-CoV-2 crosses the blood-brain barrier in mice. Nat Neurosci [Internet]. 2021 Mar;24(3):368– 78. Available from: http://dx.doi.org/10.1038/s41593-020-00771-8	This publication pertains to COVID-19 disease, but does not relate to vaccines to prevent COVID-19. The publication therefore does not present any evidence of safety concerns related to the formulation of COVID-19 vaccines.
Footnote 24: Idrees D, Kumar V. SARS-CoV-2 spike protein interactions with amyloidogenic proteins: Potential clues to neurodegeneration. Biochem Biophys Res Commun [Internet]. 2021 May 21;554:94–8. Available from: http://dx.doi.org/10.1016/j.bbrc.2021.03.100	This publication pertains to COVID-19, but does not relate to vaccines to prevent COVID-19. The publication therefore does not present any evidence of safety concerns related to the formulation of COVID-19 vaccines.
Footnote 25: Lei Y, Zhang J, Schiavon CR, He M, Chen L, Shen H, et al. SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2. Circ Res [Internet]. 2021 Apr 30;128(9):1323–6. Available	This publication pertains to the S protein, but does not relate to vaccines to prevent COVID-19. The publication therefore does not present any evidence of safety concerns related to the formulation of COVID-19 vaccines. In fact, the publication

from: http://dx.doi.org/10.1161/CIRCRESAHA.121.318902	concludes by stating: "vaccination-generated antibody and/or exogenous antibody against S protein not only protects the host from SARS-CoV-2 infectivity but also inhibits S protein-imposed endothelial injury."
Footnote 26: Zhang L, Richards A, Barrasa MI, Hughes SH, Young RA, Jaenisch R. Reverse-transcribed SARS-CoV-2 RNA can integrate into the genome of cultured human cells and can be expressed in patientderived tissues. Proc Natl Acad Sci U S A [Internet]. 2021 May 25;118(21). Available from: http://dx.doi.org/10.1073/pnas.2105968118	This publication pertains to SARS-CoV-2 infection, but does not relate to vaccines to prevent COVID-19. The publication therefore does not present any evidence of safety concerns related to the formulation of COVID-19 vaccines.
Footnote 27: Suzuki YJ, Nikolaienko SI, Dibrova VA, Dibrova YV, Vasylyk VM, Novikov MY, et al. SARS-CoV-2 spike protein-mediated cell signaling in lung vascular cells. Vascul Pharmacol [Internet]. 2021 Apr;137:106823. Available from: http://dx.doi.org/10.1016/j.vph.2020.106823	This publication pertains to SARS-CoV-2 infection, but does not relate to vaccines to prevent COVID-19. The publication therefore does not present any evidence of safety concerns related to the formulation of COVID-19 vaccines.
Footnote 28: Suzuki YJ, Gychka SG. SARS-CoV-2 Spike Protein Elicits Cell Signaling in Human Host Cells: Implications for Possible Consequences of COVID-19 Vaccines. Vaccines (Basel) [Internet]. 2021 Jan 11;9(1). Available from: http://doi.org/10.3390/vaccines901003	This publication states that "it is important to consider the possibility that the SARS-CoV-2 spike protein produced by the new COVID-19 vaccines triggers cell signaling events that promote [pulmonary arterial hypertension]," and that it important to monitor vaccinees for long-term consequences. While the publication advocates experimental animal studies, it does not provide any data suggesting that the vaccines cause any harm.

In sum, you have not demonstrated why FDA is scientifically or legally obligated to require "data on the safety and pharmacokinetic profiles of the spike protein." In other words, you have not demonstrated why it is scientifically or legally faulty for FDA to make licensure determinations without requiring the specific requested safety data on the isolated spike protein in individuals. Therefore, we deny your request.[34]

3. Petitioner's request to require data from biodistribution studies

Petitioner asks FDA to require "data from biodistribution studies investigating the actual COVID-19 vaccines." CP at 7. Petitioner asserts that data submitted thus far by Moderna and Pfizer "suggests that the vaccines distribute widely in the body, including to the liver, brain, heart, lung, adrenals, ovaries, and testes, among many other tissues." CP at 7. Petitioner further states that "instead of presenting novel biodistribution studies of the COVID-19 vaccine formulations, sponsors presented substitute studies to FDA for an EUA during the pandemic." CP at 7. Therefore, according to Petitioner, "novel biodistribution studies investigating the

[34] We note that in addition to generally requesting "data on the safety and pharmacokinetic profiles of the spike protein," you request that studies investigate the spike protein's link to certain identified health outcomes (e.g., related to coagulopathy, reproduction, etc.). See Sec. 3(c) of the CP. Because we conclude that you have not supported the need for the requested type of data that is specific to the isolated spike protein, we deny your requests that FDA require that the studies producing such data examine the identified health outcomes. It is worth pausing to acknowledge that you premise some of the health outcome data requests on information that you attribute to VAERS. While VAERS is a critical part of FDA's post-market safety monitoring system for vaccines, reports to VAERS are not confirmed to be associated with vaccination.

actual COVID-19 vaccines are necessary." CP at 7. Petitioner further states that the studies are important "to characterize long term adverse effects and better understand potential mechanism(s) of action of short and long term harms. . . " CP at 7.

FDA addressed biodistribution studies in the June 2020 Guidance in the section regarding toxicity studies. FDA recommended biodistribution studies "if the vaccine construct is novel in nature and there are no existing biodistribution data from the platform technology."[35] FDA specified that biodistribution studies may not be necessary in certain situations "if the COVID-19 vaccine candidate is made using a platform technology utilized to manufacture a licensed vaccine or other previously studied investigational vaccines and is sufficiently characterized."[36]

Petitioner has not demonstrated the need for biodistribution studies of "the actual COVID-19 vaccines." For example, it is not scientifically inappropriate to support a BLA with biodistribution data for a surrogate protein produced using the platform technology, for example if imaging on such protein can be performed to visualize the location of the protein expression. Because Petitioner has not explained why such alternative approaches cannot be used, we deny Petitioner's request.

4. Petitioner's Request to Require Data from Pharmacovigilance Systems Documenting an Investigation into Serious Adverse Events

Petitioner asks FDA to require "data from pharmacovigilance systems in the US and globally documenting a thorough investigation serious adverse events, carried out by independent, impartial individuals." CP at 8. Petitioner states that "COVID-19 vaccines have now been administered to hundreds of millions of individuals, and it is vital that all reports of SAEs [significant adverse events] are thoroughly investigated to determine whether the vaccine played any role in the SAE." CP at 8. Petitioner also states that the investigation "must be carried out by independent, impartial individuals." CP at 9. Thus, Petitioner appears to be asking for "thorough investigation" into serious adverse events.

It is unclear whether Petitioner is requesting that individual manufacturers perform the pharmacovigilance, or if Petitioner asks that FDA do so. Given that post-marketing surveillance systems are conducted both by sponsors and FDA, we interpret the request as asking that FDA ensure that both the agency and sponsors conduct the requested investigations.

Petitioner has not demonstrated any failures to conduct "thorough investigations" into post-marketing serious adverse events, so it is unclear what additional action FDA could take in response to the CP. Therefore, we deny this request.

FDA agrees that post-marketing surveillance plays an important role. FDA is monitoring the safety of the Authorized COVID-19 Vaccines through both passive and active safety surveillance systems. FDA is doing so in collaboration with the Centers for Disease Control and Prevention (CDC), the Centers for Medicare and Medicaid Services (CMS), the Department of Veterans Affairs (VA), and other academic and large non-government healthcare data systems.

[35] June 2020 Guidance, at 7.
[36] Id.

In addition, FDA participates actively in ongoing international pharmacovigilance efforts, including those organized by the International Coalition of Medicines Regulatory Authorities (ICMRA) and the World Health Organization (WHO). These efforts are in addition to the pharmacovigilance efforts being undertaken by the individual manufacturers for authorized vaccines. A coordinated and overlapping approach using state-of the art technologies has been implemented. As part of our efforts to be transparent about our COVID-19 vaccine safety monitoring activities, FDA is posting summaries of the key safety monitoring findings on the FDA website.[37]

Passive Surveillance

VAERS is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed or authorized in the United States. Passive surveillance is defined as unsolicited reports of adverse events that are sent to a central database or health authority. In the United States, these are received and entered into VAERS, which is co-managed by FDA and CDC. In the current pandemic, these reports are being used to monitor the occurrence of both known and unknown adverse events, as providers of COVID-19 vaccines are required to report serious adverse events to VAERS.

As part of FDA and CDC's multi-system approach to post-licensure and post-authorization vaccine safety monitoring, VAERS is designed to rapidly detect unusual or unexpected patterns of adverse events, also known as "safety signals." VAERS reports generally cannot be used to determine if a vaccine caused or contributed to an adverse event or illness. If the VAERS data suggest a possible link between an adverse event and vaccination, the relationship may be further studied in a controlled fashion.[38]

Anyone can make a report to VAERS, including vaccine manufacturers, private practitioners, state and local public health clinics, vaccine recipients, and their parents or caregivers. Surveillance programs like VAERS perform a critical function by generating signals of potential problems that may warrant further investigation.

Active Surveillance

Active surveillance involves proactively obtaining and rapidly analyzing information related to millions of individuals and recorded in large healthcare data systems to verify safety signals identified through passive surveillance or to detect additional safety signals that may not have been reported as adverse events to passive surveillance systems. FDA is conducting active surveillance using the Sentinel BEST (Biologics Effectiveness and Safety) System and the CMS system, and is also collaborating with other federal and non-federal partners.

BEST

[37] https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines?

[38] FDA, VAERS Overview, available at https://www.fda.gov/vaccines-blood-biologics/vaccine-adverse-events/vaers-overview

To elaborate further, the BEST system,[39] which is part of the Sentinel initiative,[40] comprises large-scale claims data, electronic health records (EHR), and linked claims-EHR databases with a data lag of approximately three months. The system makes use of multiple data sources and enables rapid queries to detect or evaluate adverse events as well as studies to answer specific safety questions for vaccines. The linked claims-EHR database makes it possible to study the safety of vaccines in sub-populations with pre-existing conditions or in pregnant women. The major partners for BEST currently are Acumen, IBM Federal HealthCare, IQVIA, and Columbia University and many affiliated partners such as MedStar Health, BlueCross BlueShield of America, the Observational Health Data Sciences and Informatics (OHDSI), OneFlorida, University of California and several others.[41]

Using BEST, CBER plans to monitor about 15 adverse events[42] that have been seen with the deployment of previous vaccines but have yet to be associated with a safety concern for an authorized COVID-19 vaccine at this time. CBER further plans to use the BEST system to conduct more in-depth analyses should a safety concern be identified from sources such as VAERS.

CMS

FDA has worked over the past several years with CMS to develop capabilities for routine and time-sensitive assessments of the safety of vaccines for people 65 years of age and older using the Medicare Claims database.[43] Because it was already in place, this system was immediately put into use for COVID-19 vaccine surveillance to monitor for adverse events.[44]

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[39] Biologics Effectiveness and Safety (BEST) System, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system

[40] FDA's Sentinel Initiative, https://www.fda.gov/safety/fdas-sentinel-initiative

[41] To confirm the utility of the BEST system for situations such as COVID-19 vaccine surveillance, a test case was conducted. This study aimed to replicate a previous study by the CDC's Vaccine Safety Datalink (VSD) (Klein et al. Pediatrics 2010) that examined the databases and analytic capabilities of the new system. The objective of this study was to test the new system's ability to reproduce the increased risk of febrile seizures in children receiving the first dose of measles-mumps-rubella-varicella (MMRV) vaccine, compared to that of MMR and varicella vaccines separately but on the same day. The results of the study met the objectives and demonstrated the ability of the BEST Initiative data network to run a complex study protocol at multiple sites using a distributed data network and the Observational Medical Outcomes Partnership Common Data Model (organizing disparate data sources into the same database design using a common format).

[42] CBER, Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring, Draft Protocol (December 31, 2020), https://www.bestinitiative.org/wp-content/uploads/2021/01/C19-Vaccine-Safety-AESI-Background-Rate-Protocol-2020.pdf

[43] CMS, Standard Analytical Files (Medicare Claims) – LDS, https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/StandardAnalyticalFiles

[44] As one example of the capabilities of this system, FDA, CMS, and CDC evaluated the risk of Guillain-Barré syndrome (GBS) following influenza vaccination after CDC's Vaccine Safety Datalink, identified safety signals suggesting an increased risk of GBS following high-dose influenza vaccinations and Shingrix vaccinations during the 2018-2019 influenza season. CBER, CDC, and CMS formed working groups in February 2019 to refine these safety signals in the CMS data.

During the current pandemic, FDA, CMS, and CDC have already used the Medicare data to publish a study showing that frailty, comorbidities, and race/ethnicity were strong risk factors of COVID-19 hospitalization and death among the U.S. elderly.[45]

In summary, in collaboration and coordination with several different partners, FDA has assembled passive surveillance systems – including VAERS – and active surveillance systems that can detect and refine safety findings with the Authorized COVID-19 Vaccines in a relatively rapid manner. These systems can also potentially be leveraged to assess safety in specific subpopulations and to assess vaccine effectiveness.

Petitioner points to a CDC webpage on COVID-19 vaccines that discusses 4,863 reports to VAERS of death after COVID-19 vaccination that describes the monitoring that is conducted in connection with such reports.[46] Petitioner suggests that this is inadequate because of an FDA response to a question posed by one of the CP signatories on the proportion of VAERS death reports for which FDA/CDC staff had reached out to families to collect follow-up information. In that response, FDA stated that "the VAERS system is not designed to determine causality of adverse events" and thus "there is not a mechanism to follow-up with families for additional details."[47] However, there are indeed procedures in place to conduct continuous monitoring of VAERS data, including deaths (though the procedures do not involve following up *with families*). When FDA and CDC receive reports of deaths in VAERS, there is a mechanism for requesting and evaluating other types of follow-up information, including associated health records, such as hospital discharge summaries, and medical and laboratory results, death certificates, and autopsy reports.[48]

5. Petitioner's Request to Include Gene Therapy Experts on the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

Petitioner requests that FDA ensure the inclusion of gene therapy experts on the VRBPAC because "there is a need to consider safety with the informed perspectives of those with expertise in gene therapies." CP at 9-10. In support of this request, Petitioner states that the vaccines produced by several manufacturers are gene based and that "[t]heir mechanism of action differs substantially from all other vaccines that have been used on populations globally, as these novel

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[45] Hector S Izurieta, David J Graham, Yixin Jiao, Mao Hu, Yun Lu, Yue Wu, Yoganand Chillarige, Michael Wernecke, Mikhail Menis, Douglas Pratt, Jeffrey Kelman, Richard Forshee, Natural History of Coronavirus Disease 2019: Risk Factors for Hospitalizations and Deaths Among >26 Million US Medicare Beneficiaries, *The Journal of Infectious Diseases*, 223: 6: 945–956 (2021), https://doi.org/10.1093/infdis/jiaa767 https://academic.oup.com/jid/article/223/6/945/6039057

[46] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.

[47] Petitioner refers to a Letter to the Editor authored by one of the CP signatories that includes questions the signatory posed to FDA, and FDA's responses. See https://www.bmj.com/content/372/bmj.n149/rr-25.

[48] See Shimabukuro et al., Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/ (stating that "For reports classified as serious, the VAERS contractor requests associated health records, including hospital discharge summaries, medical and laboratory results, and death certificates and autopsy reports for deaths. Additional MedDRA terms might be added based on information obtained through follow-up. Also, for serious reports where the patient has not recovered from the adverse event by the time the report was filed or recovery status was unknown, a follow-up letter is sent to the reporter at one year requesting information on recovery status if that information is still not known").

vaccines work on the premise of gene delivery, and may therefore be considered a type of gene therapy." CP at 9.

The VRBPAC's members are selected "among authorities knowledgeable in the fields of immunology, molecular biology, rDNA, virology; bacteriology, epidemiology or biostatistics, vaccine policy, vaccine safety science, federal immunization activities, vaccine development including translational and clinical evaluation programs, allergy, preventive medicine, infectious diseases, pediatrics, microbiology, and biochemistry."[49] Additionally, an advisory committee may consult with experts.[50] FDA may also add temporary voting members to the VRBPAC, for example to provide relevant expertise.[51] The VRBPAC's role is to advise FDA. The VRBPAC does not make regulatory decisions.

The premise of the CP is that certain actions need to be taken "before serious consideration is given to granting a BLA of any COVID-19 vaccine." CP at 1. But it is FDA, not VRBPAC, that is authorized to determine whether to approve a BLA. Indeed, the Public Health Service Act confers this authority to the Secretary of the Department of Health and Human Services, and this authority has been delegated to the Commissioner of FDA. Because FDA is authorized to approve a BLA, we do not agree that the composition of an advisory committee is determinative of whether to approve or seriously consider approving a BLA. Accordingly, we deny your request.

6. Petitioner's Request that FDA Ensure That Experts Within FDA and Amongst VRBPAC Have No Financial or Research Relationships With Any Vaccine Manufacturer's Within 36 Months

Petitioner requests that FDA "[e]nsure that the analysis of data and decisions regarding any COVID-19 vaccine BLA application are informed by experts with no financial or research relationships[52] with any vaccine manufacturers within the last 36 months, both within FDA and amongst the composition of the VRBPAC."[53] CP at 10. In support of this request, Petitioner states disclosure and transparency would demonstrate the independence of FDA decision making and that an evaluation of data by "competent individuals with independence from vaccine manufacturers" would be in the public interest.[54] CP at 10.

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[49] See FDA's Website on Vaccines and Related Biological Products Advisory Committee, https://www.fda.gov/advisory-committees/blood-vaccines-and-other-biologics/vaccines-and-related-biological-products-advisory-committee.

[50] 21 CFR § 14.31.

[51] See https://www.fda.gov/advisory-committees/vaccines-and-related-biological-products-advisory-committee/charter-vaccines-and-related-biological-products-advisory-committee.

[52] You do not describe what you mean for there to be a conflict related to "research relationships." You refer only to disclosure requirements established by the International Committee of Medical Journal Editors (ICMJE) (presumably that organization's document related to providing readers of manuscripts with information about interests that could influence how they receive scientific work), but an online form we found for ICMJE does not use or define the term "research relationship." See https://cdn-links.lww.com/permalink/jbjs/d/jbjs_2017_03_30_tashjian_e15_sdc1.pdf. That form does describe financial conflicts of interests, see id., and given the CP's statement that decisions should be made by individuals with "independence" we assume you refer to financial or employment-type conflicts.

[53] CP at 10.

[54] CP at 10.

FDA acknowledges the value in maintaining a positive public perception of how FDA conducts its activities and ensuring that the decisions FDA employees make, and actions they take, neither are, nor appear to be, tainted by any conflict of interest. Ethical requirements for both advisory committee and staff are described in statute and regulation.[55]

FDA has addressed the evaluation of financial interests by special Government employees (SGEs) and FDA employees in the 2014 Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers[56] (Financial Issues Guidance) and has addressed the evaluation of appearance issues in the 2016 draft Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Procedures for Evaluating Appearance Issues and Granting Authorizations for Participation in FDA Advisory Committees (Appearance Issues Draft Guidance).[57] The 2016 draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. As described in the Appearance Issues Draft Guidance, "[t]o protect the credibility and integrity of advisory committee advice, FDA screens advisory committee members carefully for two categories of potentially disqualifying interests or relationships: (1) current financial interests that may create a recusal obligation under Federal conflict of interest laws; and (2) other interests and relationships that do not create a recusal obligation under Federal conflict of interest laws but that may create the appearance that a member lacks impartiality, known as 'appearance issues.'" The Appearance Issues Guidance explicitly contemplates that a Research Relationship might raise an appearance issue.[58]

FDA employees also are subject to strict ethical requirements.[59] FDA employees, as well as their spouses and minor children, are prohibited from holding financial interests, like stock, in certain businesses regulated by FDA. This includes many companies working in the drug, biologic, medical device, food, and tobacco industries, among others.[60] In addition, certain restrictions apply to FDA employees working on particular matters involving parties with whom the employee has served as officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee.[61]

Although both the VRBPAC members and FDA employees are subject to ethical requirements, the requirements do not involve a 36-month prohibition. For example, FDA is authorized by statute to grant waivers to allow individuals with potentially conflicting financial interests to participate in meetings where it concludes, after close scrutiny, that certain criteria are met.[62] In addition, the restrictions that apply to FDA employees working on particular matters involving parties with whom the employee has served as officer, director, trustee, general partner, agent,

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[55] See, e.g., 18 U.S.C. § 208; See also the description of Ethics Laws and Regulations on FDA's website, available at: https://www.fda.gov/about-fda/ethics/ethics-laws-and-regulations

[56] https://www.fda.gov/media/83188/download. "Most FDA advisory committee members are appointed as SGEs." Financial Issues Guidance at 3.

[57] https://www.fda.gov/media/98852/download.

[58] See Appearance Issues Draft Guidance at 14-15.

[59] For a summary of relevant requirements, see the description of Ethics Laws and Regulations on FDA's website https://www.fda.gov/about-fda/ethics/ethics-laws-and-regulations.

[60] See Prohibited Financial Interests for FDA Employees, https://www.fda.gov/about-fda/ethics/prohibited-financial-interests-fda-employees.

[61] 5 CFR § 2635.502.##

[62] See 18 U.S.C. § 208(b)(1) and (b)(3).

attorney, consultant, contractor or employee apply when the employee has served *within the last year*--but not longer.

In evaluating your request, we are guided by these laws and regulations, which do not contain a 36-month prohibition. We also note that you have not demonstrated that any FDA employees or members of the VRBPAC have been improperly involved in the agency's review of COVID-19 vaccines. We are also guided by our consideration of one of the purposes served by an FDA advisory committee, which is that it permits the agency access to a range of perspectives from experts with the most current knowledge. We believe that applying our existing standards for conflict of interest will address the perception concern that the CP articulates, while appropriately balancing the agency's need for current outside expertise. Accordingly, we deny your request.

7. Petitioner's Request to Revise the 2020 Guidance to Require 2 Years of Follow-Up

Petitioner requests that FDA "[c]onfirm, in revised Guidance, that the FDA expects a minimum of 2 years of follow-up of participants enrolled in pivotal clinical trials, even if trials are unblinded and lack a placebo control." CP at 4. You state that "two year follow-up from trials allows the detection of commonly experienced longer-term adverse effects that may not manifest until many months following vaccination" and would add to the data collection in clinical trials in certain ways that you identify. CP at 4.

FDA's June 2020 Guidance describes FDA's expectations for follow-up of participants enrolled in clinical trials.[63] FDA does not at this time see a need to revise its guidance documents, because FDA may communicate to individual sponsors whether there is a need to support a BLA with a particular duration of follow-up for a clinical trial. While guidance documents allow the agency to articulate its interpretation of or policy on a regulatory matter (21 CFR § 10.115(b)), there are also times where FDA's advice would be specific to an individual manufacturer.

In addition, we note that there are many reasons why it may be appropriate to license some vaccines based on follow-up of participants for less than two years. For example, if a clinical trial enrolls subjects rapidly and the primary endpoint is the incidence of a disease such as COVID-19 which occurs frequently, cases may accumulate quickly and may allow FDA to assess the benefit-risk profile of the vaccine based on a shorter clinical trial duration and participant follow-up. By contrast, if a clinical trial enrolls subjects more slowly and assesses a disease with lower incidence, more time may be needed to accumulate a database that allows statistically meaningful comparisons to be drawn between the vaccine and control groups. FDA's benefit-risk analysis may reasonably take into account the historical experience with vaccines, and the fact that most adverse events that are plausibly linked to vaccination occur within two months of vaccination.[64] Furthermore, vaccine trials involve different types of endpoints, with some trials focusing on immunogenicity endpoints and some focusing on disease endpoints. All of these features impact the type and duration of data needed to evaluate the benefits and risks of a vaccine.

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[63] See, e.g., June 2020 Guidance at 12.

[64] Table VI. National Vaccine Injury Compensation Program. Rockville, MD: Health Resources and Services Administration, 2017 (https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf. opens in new tab).

For all of these reasons, we deny Petitioner's request.

8. **Petitioner's Request that FDA Revise its Guidance Document to Address Safety Data from Individuals Receiving more than 2 Doses**

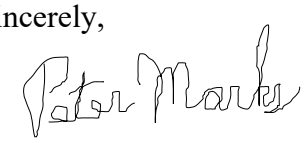
Petitioner states that FDA should "[c]larify in revised Guidance that safety data from individuals receiving more than 2 vaccine doses must be submitted by vaccine manufacturers." CP at 9. Petitioner states that the safety profile of multiple doses must be considered. CP at 9.

FDA does not at this time see a need to revise its guidance documents, because FDA may communicate to individual sponsors whether there is a need to provide the agency with data to support the possible use of more than 2 vaccine doses. While guidance documents allow the agency to articulate its interpretation of or policy on a regulatory matter (21 CFR § 10.115(b)), there are also times where FDA's advice would be specific to an individual manufacturer. Accordingly, we deny Petitioner's request.

a. Conclusion

FDA has considered Petitioner's requests. For the reasons given in this letter, FDA denies the requests in Petitioner's citizen petition. Therefore, we deny the CP in its entirety.

Sincerely,



Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

cc: Dockets Management Staff

Appendix I: Aspects of Vaccine Development and Process for Licensure

A. Vaccines are Biologics and Drugs

Vaccines are both biological products under the Public Health Service Act (PHS Act) (42 U.S.C. § 262) and drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 321). The PHS Act defines a "biological product" as including a "vaccine…or analogous product…applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1). The FD&C Act defines drug to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man." 21 U.S.C. § 321(g)(1)(B).

Under the PHS Act, a biological product may not be introduced or delivered for introduction into interstate commerce unless a biologics license is in effect for the product. 42 U.S.C. § 262(a)(1)(A).

B. Clinical Investigations of Vaccines

Before a vaccine is licensed (approved) by FDA and can be used by the public, FDA requires that it undergo a rigorous and extensive development program that includes laboratory research, animal studies, and human clinical studies to determine the vaccine's safety and effectiveness.

The PHS Act and the FD&C Act provide FDA with the authority to promulgate regulations that provide a pathway for the study of unapproved new drugs and biologics. 42 U.S.C. § 262(a)(2)(A) and 21 U.S.C. § 355(i). The regulations on clinical investigations require the submission of an Investigational New Drug application (IND), which describes the protocol, and, among other things, assures the safety and rights of human subjects. These regulations are set out at 21 CFR Part 312. See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).

The regulations provide that, once an IND is in effect, the sponsor may conduct a clinical investigation of the product, with the investigation generally being divided into three phases. With respect to vaccines, Phase 1 studies typically enroll fewer than 100 participants and are designed to look for very common side effects and preliminary evidence of an immune response to the candidate vaccine. Phase 2 studies may include up to several hundred individuals and are designed to provide information regarding the incidence of common short-term side effects, such as redness and swelling at the injection site or fever, and to further describe the immune response to the investigational vaccine. If an investigational new vaccine progresses past Phase 1 and Phase 2 studies, it may progress to Phase 3 studies. For Phase 3 studies, the sample size is often determined by the number of subjects required to establish the effectiveness of the new vaccine, which may be in the thousands or tens of thousands of subjects. Phase 3 studies are usually of sufficient size to detect less common adverse events.

If product development is successful and the clinical data are supportive of the proposed indication, the completion of all three phases of clinical development can be followed by submission of a Biologics License Application (BLA) pursuant to the PHS Act (42 U.S.C. § 262(a)), as specified in 21 CFR § 601.2.

C. Biologics License Applications

A BLA must include data demonstrating that the product is safe, pure, and potent and that the facility in which the product is manufactured "meets standards designed to assure that the biological product continues to be safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i). FDA does not consider an application to be filed until FDA determines that all pertinent information and data have been received. 21 CFR § 601.2. FDA's filing of an application indicates that the application is complete and ready for review but is not an approval of the application.

Under § 601.2(a), FDA may approve a manufacturer's application for a biologics license only after the manufacturer submits an application accompanied by, among other things, "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency." The BLA must provide the multidisciplinary FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc.) with the Chemistry, Manufacturing, and Controls (CMC)[65] and clinical information necessary to make a benefit-risk assessment, and to determine whether "the establishment(s) and the product meet the applicable requirements established in [FDA's regulations]." 21 CFR § 601.4(a).

FDA generally conducts a pre-license inspection of the proposed manufacturing facility, during which production of the vaccine is examined in detail. 42 U.S.C. § 262(c). In addition, FDA carefully reviews information on the manufacturing process of new vaccines, including the results of testing performed on individual vaccine lots.

FDA scientists and physicians evaluate all the information contained in a BLA, including the safety and effectiveness data and the manufacturing information, to determine whether the application meets the statutory and regulatory requirements. FDA may also convene a meeting of its advisory committee to seek input from outside, independent, technical experts from various scientific and public health disciplines that provide input on scientific data and its public health significance.

As part of FDA's evaluation of a vaccine as a whole, FDA takes all of a vaccine's ingredients into account (including preservatives and adjuvants). FDA licenses a vaccine only after the Agency has determined that the vaccine is safe and effective for its intended use, in that its benefits outweigh its potential risks.

[65] Also referred to as Pharmaceutical Quality/CMC.

Appendix II: Aspects of Vaccine Postmarketing Safety Monitoring

Post-marketing surveillance of vaccine safety is crucial to detect any rare, serious, or unexpected adverse events, as well as to monitor vaccine lots. Manufacturers often conduct post-marketing observational studies. However, FDA also uses multiple tools and databases to evaluate the safety of vaccines after they have been licensed and used in the general population.

The Vaccine Adverse Event Reporting System (VAERS) is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed in the United States. VAERS is co-administered by FDA and the Centers for Disease Control and Prevention (CDC). Anyone can make a report to VAERS, including vaccine manufacturers, private practitioners, State and local public health clinics, vaccine recipients, and their parents or caregivers. Surveillance programs like VAERS perform a critical function by generating signals of potential problems that may warrant further investigation.

It is often difficult to determine with certainty if a vaccine caused an adverse event reported to VAERS. Many events that occur after vaccination can happen by chance alone. Some adverse events are so rare that their association with a vaccine is difficult to evaluate. In addition, VAERS often receives reports where there is no clear clinical diagnosis. FDA draws upon multiple sources of data and medical and scientific expertise to assess the potential strength of association between a vaccine and a possible adverse event.

Monitoring and analysis of VAERS reports typically includes daily in-depth medical review of all serious reports, statistical data mining techniques, and epidemiological analysis. We look for patterns and similarities in the onset timing and clinical description. We review published literature to understand possible biologic hypotheses that could plausibly link the reported adverse event to the vaccine. We review the pre-licensure data and any other post-marketing studies that have been conducted. We also consider "background rate," meaning the rate at which a type of adverse event occurs in the unvaccinated general population. When necessary, we discuss the potential adverse event with our federal and international safety surveillance partners. We also carefully evaluate unusual or unexpected reports, as well as reports of "positive re-challenges" (adverse events that occur in the same patient after each dose received). When there is sufficient evidence for a potential safety concern we may proceed to conduct large studies, and we may coordinate with our federal, academic and private partners to further assess the potential risk after vaccination. In addition, when potential safety issues arise, they are often presented to various U.S. government advisory committees, including the Vaccines and Related Biological Products Advisory Committee, the Advisory Committee on Immunization Practices, the Vaccines Advisory Committee, and the Advisory Committee on Childhood Vaccines, and are often discussed with experts from other countries and from the World Health Organization (WHO). Federal agencies that assist in population-based vaccines safety studies include the Centers for Medicaid and Medicare (CMS), the Department of Defense (DoD), and the Indian Health Services (IHS). In addition, we generally communicate and work with international regulatory authorities and international partners to conduct studies in vaccine safety.

The Vaccine Safety Datalink (VSD) project has actively monitored vaccine safety in more than 9.1 million people nationwide, over 3% of the US population. The VSD can monitor vaccine safety with near real-time surveillance systems, which is particularly important for new vaccines. If there is a vaccine safety signal in the VSD, chart reviews and case series analyses are done

when assessing the possible association between a vaccine and an adverse event. If needed, VSD is able to use its large health care database to further evaluate specific vaccine safety concerns.

The Clinical Immunization Safety Assessment (CISA) is a national network of six medical research centers with expertise conducting clinical research related to vaccine safety. The goals of CISA are: to study the pathophysiologic basis of adverse events following immunization using hypothesis-driven protocols; to study risk factors associated with developing an adverse event following immunization using hypothesis-driven protocols, including genetic host-risk factors; to provide clinicians with evidence-based guidelines when evaluating adverse events following immunization; to provide clinicians with evidence-based vaccination or revaccination guidelines; and to serve as a regional referral center to address complex vaccine safety inquiries. Advances in genetics and immunology continue to help us further assess the safety of vaccines, and FDA has established a genomics evaluation team for vaccine safety.

Finally, the Sentinel Initiative is a national electronic system that will continue to improve FDA's ability to track the safety of medical products, including vaccines. Launched in May 2008 by FDA, the Sentinel System will enable FDA to actively query diverse automated healthcare data holders – like electronic health record systems, administrative and insurance claims databases, and registries – to evaluate possible safety issues quickly and securely. The Sentinel Initiative will cover 100 million people in the U.S. It is also anticipated that Sentinel will facilitate the development of active surveillance methodologies related to signal detection, strengthening, and validation.