IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MISSOURI
EASTERN DIVISION

STATE OF MISSOURI, et al., Plaintiffs, v. JOSEPH R. BIDEN, et al. Defendants.	No. 4:21-cv-01300-DDN

DEFENDANTS' OPPOSITION TO PLAINTIFFS' MOTION FOR A PRELIMINARY INJUNCTION

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Regulations

Other Authorities

INTRODUCTION

The United States is in the midst of the most serious public health crisis it has faced in at least a century. To date, COVID-19 has infected more than 47 million Americans, hospitalized more than 3 million, and killed over 761,000. *See* Centers for Disease Control and Prevention (CDC), COVID Data Tracker Weekly Review, https://perma.cc/UGE3-XZ7Q (updated Nov. 17, 2021); CDC, COVID DATA Tracker – Cases, Deaths, and Testing (updated Nov. 15, 2021), https://perma.cc/2LZK-7WGX. More than a year and a half into the COVID-19 pandemic, approximately 70,000 new cases are reported in the United States every day. *See* COVID Data Tracker Weekly Review, *supra*.

Since the pandemic's earliest days, there has been broad agreement—from public health experts and leaders across the political spectrum—that the pandemic will not end until safe and effective vaccines are broadly administered across the population. Three such vaccines—one developed by Pfizer, Inc. and BioNTech; another by Moderna TX, Inc.; and a third by Janssen Biotech, Inc., a subsidiary of Johnson & Johnson—are now widely available in the United States. Hundreds of millions of doses have been administered, and there is no question that the vaccines are safe and highly effective. Yet as of November 5, 2021, only 58.2% of adults in the United States are fully vaccinated. *See id.* And in October 2021—many months after COVID-19 vaccines became widely available to adults at no cost—over 40,000 Americans died of COVID-19. *See* CDC, COVID DATA Tracker – Daily and Total Trends (updated Nov. 4, 2021), https://perma.cc/B3JG-99AL.

The illness and mortality caused by COVID-19 have led to serious disruptions for organizations and contractors across the United States, and the federal government is no exception. Accordingly, on September 9, 2021, acting as Chief Executive Officer of the Executive Branch, the

President issued an executive order aimed at preventing disruptions in the provision of government services by federal contractors by combatting the spread of COVID-19. See Ensuring Adequate COVID Safety Protocols for Federal Contractors, Exec. Order No. 14,042 (EO 14,042), 86 Fed. Reg. 50,985 (Sept. 14, 2021). EO 14,042 instructs federal agencies, "to the extent permitted by law," to ensure that certain federal contracts include a clause requiring the contractor or subcontractor to comply with COVID-19 safety protocols published by the Safer Federal Workforce Task Force (Task Force), and approved by the Director of the Office of Management and Budget (OMB) in a determination published in the Federal Register. 86 Fed. Reg. at 50,985. Those protocols require full vaccination by all employees (subject to legally required exemptions) at a workplace in which individuals working on or in connection with government contracts in which the clause required by EO 14,042 is present. OMB, Determination of the Acting OMB Director Regarding the Revised Safer Federal Workforce Task Force Guidance for Federal Contractors and the Revised Economy & Efficiency Analysis, 86 Fed. Reg. 63,418 (Nov. 16, 2021). For the type of contracts covered by the EO, federal agencies are required to include the safety protocols in "any new contract," "new solicitation for a contract," "extension or renewal of an existing contract," and "exercise of an option on an existing contract." EO 14,042 § 5. The deadline for full vaccination by covered contractor employees is January 18, 2022.

Plaintiff States have sued the President, the United States, and more than two dozen federal agencies and officials. Plaintiffs challenge Executive Order 14,042, which directs federal government contracts to include a clause requiring certain COVID safety protocols—including vaccination requirements—in "any new contract," "new solicitation for a contract," "extension or renewal of an existing contract," and "exercise of an option on an existing contract." Executive Order 14,042, 86 FR 50985 (Sept. 9, 2021) ("Executive Order" or "EO").

Plaintiffs[1] ask this Court to exercise its extraordinary emergency powers to enjoin this EO across the country—even outside the boundaries of the Plaintiff States. *See* Mem. in Support of Pls.' Mem. for Prelim. Inj. ECF No. 9 ("Pls.' Mem."). But this Court should reject Plaintiffs' argument that the President has no power to direct federal contracting—an argument that conflicts with more than 50 years of precedent. Their procedural and notice arguments are meritless and now are moot because the Director of the Office of Management and Budget issued a Notice last week, including opening up a period for comments. And the constitutional claims raised by Plaintiffs have been considered and rejected by courts many times over.

Plaintiffs' motion for a preliminary injunction should be denied.

BACKGROUND AND PROCEDURAL HISTORY

I. The COVID-19 Pandemic

In January 2020, the emergence of the novel coronavirus SARS-CoV-2 caused the Secretary of Health and Human Services to declare a public health emergency, and in March 2020, the President declared a national emergency to contain and combat the virus. *See* Declaring a Nat'l Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak, Proclamation No. 9994, 85 Fed. Reg. 15,337 (Mar. 18, 2020). SARS-CoV-2 causes a respiratory disease known as COVID-19, *id.*, which "spreads when an infected person breathes out droplets and very small particles that contain the virus," CDC, How COVID-19 Spreads (updated July 14, 2021), https://perma.cc/9MSV-BS5N.

In July 2021, the United States began to experience "a rapid and alarming rise in . . . COVID-19 case and hospitalization rates," driven by an especially contagious strain of SARS-

[1] Plaintiff States are Missouri, Nebraska, Alaska, Arkansas, Iowa, Montana, New Hampshire, North Dakota, South Dakota, and Wyoming.

CoV-2 known as the Delta variant. *See* CDC, Delta Variant: What We Know About the Science (updated Aug. 26, 2021), https://perma.cc/5CAA-WC8A. As of this filing, community transmission rates of SARS-CoV-2 remain high in 39 states, substantial in other 10 states and the District of Columbia, and moderate in the remaining state.[2] *See* CDC, COVID DATA Tracker – Cases, Deaths, and Testing (updated Nov. 15, 2021), https://perma.cc/2LZK-7WGX.

II. The Development and Authorization of COVID-19 Vaccines

Currently, three manufacturers offer vaccines approved or authorized for use in the United States by the Food and Drug Administration (FDA). *See* https://perma.cc/2N5P-22F6. The FDA has authority to review and approve "biological products," including vaccines, as safe and effective for introduction into interstate commerce for their intended uses. *See* 42 U.S.C. § 262(a)(1), (i)(1). Under § 564 of the Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, the FDA also may issue an "emergency use authorization" (EUA) even before such approval, which permits the marketing of vaccines (and other products) "intended for use" in responding to a public health emergency.

In March 2020, the Secretary of Health and Human Services determined that "circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic." EUA Declaration, 85 Fed. Reg. 18,250, 18,250–51 (Apr. 1, 2020). Based on that determination, the FDA issued EUAs in December 2020 for the Pfizer-BioNTech and Moderna vaccines, and a third EUA in February 2021 for the Janssen vaccine. *See* Oct. 29, 2021 Letter of Authorization from FDA to Pfizer Inc., https://perma.cc/YY3Q-JGW4 (Pfizer EUA Letter) (revising and reissuing the December 2020 EUA); Oct. 20, 2021 Letter of

[2] The Court can judicially notice these statistics and other facts on government websites. *See Tellabs, Inc. v. Makor Issues & Rts., Ltd.*, 551 U.S. 308, 322–23 (2007); *Swindol v. Aurora Flight Sci. Corp.*, 805 F.3d 516, 518-19 & n.2 (5th Cir. 2015).

Authorization from FDA to ModernaTX, Inc., https://perma.cc/LN7L-AE6D (Moderna EUA Letter) (same); Oct. 20, 2021 Letter of Authorization from FDA to Janssen Biotech, Inc., https://perma.cc/R7HA-Z6BD (Janssen EUA Letter) (revising and reissuing the February 2021 EUA). These EUAs are based on the FDA's review of extensive safety and efficacy data, including from a Pfizer clinical trial with approximately 46,000 participants, a Moderna clinical trial with approximately 30,000 participants, and a Janssen clinical trial with approximately 43,000 participants. *See* Pfizer EUA Letter at 4; Moderna EUA Letter at 2; Janssen EUA Letter at 2.

On August 23, 2021, the Pfizer-BioNTech COVID-19 vaccine obtained FDA approval, under the name Comirnaty, for people aged 16 years and older. *See* Ex. 1 ¶ 6, Decl. of Peter Marks, M.D., Ph.D.[3] This means that the vaccine has completed "the agency's standard process for reviewing the quality, safety and effectiveness of medical products." FDA, News Release – FDA Approves First COVID-19 Vaccine (Aug. 23, 2021), https://perma.cc/J9NV-92VH. In approving Comirnaty, the FDA determined that the vaccine was 91.1% effective in preventing COVID-19 disease and between 95% and 100% effective in preventing severe COVID-19, based on an analysis of effectiveness data from approximately 20,000 vaccine and 20,000 placebo recipients. FDA, Comirnaty Approved Prescribing Information at 7, 15–18 (revised Aug. 2021), https://perma.cc/53H8-UG3C. The FDA concluded the product is safe based on data from approximately 12,000 vaccine recipients who were followed for safety outcomes for at least six months after their second dose, as well as safety information from the millions of vaccine doses administered under the EUA. *Id.* at 12.

[3] The Marks Declaration, submitted in *Doe v. Austin*, Civil No. 3:21-cv-01211 (N.D. Fl.), a challenge to FDA action filed in the Northern District of Florida, is offered here to provide useful background on the authorization and subsequent approval of the Pfizer-BioNTech vaccine.

III. Vaccination Requirements for Federal Contractors

On September 9, 2021, President Biden issued EO 14,042 to "promote[] economy and efficiency in Federal procurement by ensuring that the parties that contract with the Federal Government provide adequate COVID-19 safeguards to their workers performing on or in connection with a Federal Government contract or contract-like instrument." *See* EO 14,042 § 1. The President determined that new safeguards would "decrease worker absence, reduce labor costs, and improve the efficiency of contractors and subcontractors at sites where they are performing work for the Federal Government." *Id*. Those specific safeguards would be set forth in guidance issued by the Safer Federal Workforce Task Force ("Task Force"). *Id*. But that guidance would not be binding until the OMB Director, acting pursuant to a delegation the President's statutory authority, approves the guidance and determines that the guidance "will promote economy and efficiency in Federal contracting if adhered to by Government contractors and subcontractors" to the OMB Director *Id*. § 2(c) (citing 3 U.S.C. § 301).

EO 14,042 is a directive from the President, essentially acting as the U.S. Government's Chief Executive Officer, to federal executive departments and agencies, "to the extent permitted by law," to incorporate a clause into certain types of contracts—new contracts, new solicitations for a contract, extensions or renewals of an existing contract, and exercises of an option on an existing contract—if they also fall into one of the following categories (all categories together, "covered contracts"): (i) a procurement contract for services, construction, or a leasehold interest in real property; (ii) a contract for services covered by the Service Contract Act, 41 U.S.C. § OMB, Determination of the Acting OMB Director Regarding the Revised Safer Federal Workforce Task Force Guidance for Federal Contractors and the Revised Economy & Efficiency

Analysis, 86 Fed. Reg. 63,418 (Nov. 16, 2021). 6701 *et seq.*; (iii) a contract for concessions, including any concessions contract excluded by Department of Labor regulations at 29 C.F.R. § 4.133(b); or (iv) a contract entered into with the Federal government in connection with Federal property or lands and related to offering services for Federal employees, their dependents, or the general publicEO 14,042 § 5(a). The required clause "shall specify that the contractor or subcontractor shall, for the duration of the contract, comply with all guidance for contractor or subcontractor workplace locations published by" the Task Force, provided the guidance is approved by the OMB Director, as described above. *Id*. at § 2(a). The mandatory clause also "shall apply to any workplace locations (as specified by the Task Force Guidance) in which an individual is working on or in connection with a Federal Government contract[.]" *Id.*

The EO, however, is targeted and contains exceptions. As relevant here, it does not apply to contracts below the special acquisition threshold, *id*. at § 5(a), which is currently $250,000. Fed. Acquisition Reg. 2.101, Definitions, *available* at https://www.acquisition.gov/far/2.101. Moreover, although EO 14,042 provides that "agencies are strongly encouraged, to the extent permitted by law, to ensure that the safety protocols required under [existing] contracts . . . are consistent with" the Task Force Guidance, it includes no authority to force conforming changes to existing contracts. *Id*. at § 6(c).

The Task Force issued guidance under EO 14,042 on September 24, 2021.[4] Task Force, COVID-19 Workplace Safety: Guidance for Federal Contractors and Subcontractors (September Contractor Guidance), https://perma.cc/H2MY-K8RT. Exercising the authority delegated to her by the President, the Acting OMB Director made the statutorily required determination that the

[4] Throughout, "Task Force Guidance" means the operative guidance at the time.

Task Force Guidance would promote economy and efficiency in federal contracting. *See* Determination of the Promotion of Economy and Efficiency in Federal Contracting Pursuant to Executive Order No. 14,042, 86 Fed. Reg. 63,691, 53,691–92 (Sept. 28, 2021).[5]

On November 10, 2021, the Task Force issued revised Task Force Guidance. Determination of the Acting OMB Director Regarding the Revised Safer Federal Workforce Task Force Guidance and the Revised Economy & Efficiency Analysis, unpublished version available online at https://perma.cc/9Q3S-5WMA ("OMB Determination"). At the same time, OMB submitted a new Determination by the OMB Director. 86 Fed. Reg. 63,418. The new Determination rescinded and superseded the previous September 24 notice (thus superseding the earlier Task Force Guidance); included a determination by the Acting OMB Director, exercising the authority delegated to her by the President, that the Task Force Guidance would promote economy and efficiency in federal contracting; provided the revised Task Force Guidance; included economic analysis of the COVID-19-workplace safety protocols and the effect on economy and efficiency in federal procurement; and addressed procedural requirements. *Id.*

The Task Force Guidance requires federal contractors that are party to a covered contract to "ensure that all covered contractor employees are fully vaccinated for COVID-19, unless the employee is legally entitled to an accommodation." *Id.* at 9. "Covered contractor employees means any full-time or part-time employee of a covered contractor working on or in connection

[5] The Task Force Guidance determined that covered contractor and subcontractor employees should be vaccinated against COVID-19, except insofar as any such employee was legally entitled to an accommodation. *See* Sept. Contractor Guidance at 5–6. Consistent with the EO, the Task Force Guidance set forth a phase-in period for the new requirements to be added to federal contracts, generally keyed to new contracts awarded on or after November 14 and any changes to existing contracts made on or after October 15. *See id.* at 12.

with a covered contract or working at a covered contractor workplace." *Id.* at 6. A covered contractor workplace is "a location controlled by a covered contractor at which any employee of a covered contractor working on or in connection with a covered contract is likely to be present during the period of performance for a covered contract." *Id.*

Covered contractor employees subject to the requirement must be fully vaccinated[6] no later than January 18, 2022. *Id.* at 9. After that date, covered contractor employees not subject to the requirement "must be fully vaccinated by the first day of the period of performance on a newly awarded covered contract, and by the first day of the period of performance on an exercised option or extended or renewed contract when the clause has been incorporated into the covered contract." *Id.* Covered contractors oversee compliance with the Task Force Guidance. Federal law may in some cases require covered contractor employers to provide accommodation to contractor employees "who communicate to the covered contractor that they are not vaccinated against COVID-19 because of a disability (which would include medical conditions) or because of a sincerely held religious belief, practice, or observance" may be provided accommodations by the covered contractor. *Id.* at 9–10.

IV. Procedural History

On October 29, 2021, Plaintiffs filed this lawsuit to challenge EO 14,042, the Task Force Guidance, OMB's determination, and the FAR Memo. Compl., ECF No. 1. Plaintiffs bring 12 claims against Defendants, *id.* ¶¶ 91–186, and seek declaratory and injunctive relief, *id.* Prayer

[6] Under the Task Force Guidance, "people are considered fully vaccinated if they have received COVID-19 vaccines currently approved or authorized for emergency use by the FDA (Pfizer-BioNTech, Moderna, and Johnson & Johnson/Janssen COVID-19 vaccines) or COVID-19 vaccines that have been listed for emergency use by the World Health Organization (e.g., AstraZeneca/Oxford)." Nov. Notice at 8.

for Relief. On November 4, prior to the issuance of the November OMB Determination, Plaintiffs moved for a preliminary injunction. ECF No. 8.

LEGAL STANDARDS

"A preliminary injunction is an extraordinary remedy never awarded as of right." *Winter v. Nat. Res. Def. Council, Inc.*, 555 U.S. 7, 24 (2008) (citation omitted). To justify this "drastic remedy," the movants must "clearly establish[] the burden of persuasion" on the following four elements: (1) Plaintiffs have a substantial likelihood of success on the merits; (2) there is a substantial threat that Plaintiffs will suffer irreparable injury absent an injunction; (3) the threatened injury to Plaintiffs outweighs the damage an injunction would cause to Defendants; and (4) the injunction would not be adverse to the public interest. *Adventist Health Sys./SunBelt, Inc. v. United States Dep't of Health & Hum. Servs.* — F. 4th. —, No. 21-1589, 2021 WL 5170810, at *5 (8th Cir. Nov. 8, 2021). "Failure to show any of the four factors is fatal[.]" *ACLU of Fla., Inc. v. Miami-Dade Cty. Sch. Bd.*, 557 F.3d 1177, 1198 (11th Cir. 2009).

ARGUMENT

I. Plaintiffs are unlikely to succeed on the merits.

A. Plaintiffs are not likely to show that the President lacks authority to direct federal government contracting.

Plaintiffs first argue that the President lacks authority to issue binding guidance for government contracts. Pls.' Mem. at 16. This argument ignores that Congress specifically authorized the President to direct federal procurement in the Federal Property and Administrative Services Act, FPASA. 40 U.S.C. § 121(a). While Plaintiffs claim that the FPASA does not grant the President such authority, they cite no opinions interpreting the FPASA in the novel manner they are proposing. Indeed, Plaintiffs' position ignores the President's role as manager of the Executive

Branch and more than half a century of precedent from all three branches of our constitutional system.

Since the 1960s, federal appellate courts have routinely held that the FPASA authorizes the president to manage government contracting through executive orders. *See, e.g.*, *Farmer v. Phila. Elec. Co.*, 329 F.2d 3, 7 (3d Cir. 1964); *Farkas v. Texas Instrument, Inc.*, 375 F.2d 629, 632 (5th Cir. 1967). Courts have concluded, for example, that FPASA authorizes the President to require government contractors to comply with wage and price controls, *AFL-CIO v. Kahn*, 618 F.2d 784 (D.C. Cir. 1979) (en banc), to post notices at all of their facilities informing employees that they cannot be forced to join a union or to pay mandatory dues for costs unrelated to representational activities, *UAW-Lab. Emp. & Training Corp. v. Chao*, 325 F.3d 360, 366 (D.C. Cir. 2003), and to require contractors to confirm employees' immigration status through e-Verify, *Chamber of Com. of U.S. v. Napolitano*, 648 F. Supp. 2d 726, 729 (D. Md. 2009). *See also City of Albuquerque v. U.S. Dep't of Interior*, 379 F.3d 901 (10th Cir. 2004) (urban renewal); *AFGE v. Carmen*, 669 F.2d 815 (D.C. Cir. 1981) (conservation of gasoline during an oil crisis). Indeed, even cases relied on by Plaintiffs confirm that "the Procurement Act does vest broad discretion in the President." *Chamber of Com. of U.S. v. Reich*, 74 F.3d 1322, 1330, 1334 (D.C. Cir. 1996) (affirming the "President's authority to pursue 'efficient and economic' procurement" through EOs, but holding the challenged order conflicted with the National Labor Relations Act).

Plaintiffs ask the Court to adopt their cramped interpretation of the FPASA by purportedly relying on the text of the statute. But the text is quite broad—the FPASA authorizes the President to "prescribe such policies and directives, not inconsistent with the provisions of this Act, as he shall deem necessary to effectuate the provisions of said Act." *Chao*, 325 F.3d at 366 (quoting 40 U.S.C. § 486(a) (2000) (now codified as amended at 40 U.S.C. § 121)). The

President is given broad discretion to supervise government contracting "as he shall deem necessary" so long as the President does not act "inconsistent[ly] with the provisions" of the FPASA. Courts have "read this as requiring that the executive order have a 'sufficiently close nexus' to the values of providing the government an 'economical and efficient system for . . . procurement and supply.'" *Chao*, 325 F.3d at 366 (quoting *Kahn*, 618 F.2d at 788, 792); *see also Liberty Mut. Ins. Co. v. Friedman*, 639 F.2d 164, 169 (4th Cir. 1981) (citing 40 U.S.C. § 101 *et seq.*).[7] And as discussed below, the challenged policies satisfy this nexus requirement.

Plaintiffs' argument that the President lacks authority to direct government contracting is further undermined by Congress's implicit endorsement of an expansive view of the President's power under the FPASA. Presidents have regularly exercised their authority under the FPASA since it was enacted. *See Kahn*, 618 F.2d 784, 790–91 ("Since 1941, though, the most prominent use of the President's authority under the FPASA has been a series of anti-discrimination requirements for Government contractors"); *see also, e.g.*, EO No. 12072, 43 FR 36869 (Aug. 16, 1978); EO 13465, 73 FR 33285 (June 11, 2008); EO 13950, 85 FR 60683 (Sept. 22, 2020). "Past [Presidential] practice does not, by itself, create power, but 'long-continued practice, known to and acquiesced in by Congress, would raise a presumption that the [action] had been [taken] in pursuance of its consent.'" *Dames & Moore v. Regan*, 453 U.S. 654, 686 (1981). "[T]he President's view of his own authority under a statute is not controlling, but when that view has been

[7] Plaintiffs likewise fail to provide any legal authority that the President's authority to "prescribe[e] policies and directives" is less expansive than the GSA Administrator's authority to "prescribe regulations." Pls.' Mem. at 17; (citing 40 U.S.C. § 121(a) and (d)). The words "regulation," "policy," and "directive" are neither statutorily defined words nor terms of art, and cases use them interchangeably. *See, e.g.*, *Liberty Mut.*, 639 F.2d at 173 (Butzner, J., concurring-in-part and dissenting-in-part) ("Implicit in [FPASA], I believe, is authorization for the President to promulgate orders and regulations . . . ."). As a matter of ordinary meaning, all three are synonyms. *See, e.g.*, *Regulation*, Oxford English Dictionary (3d ed. 2009) ("[A] directive established and maintained by an authority.").

acted upon over a substantial period of time without eliciting Congressional reversal, it is entitled to great respect." *Kahn*, 618 F.2d at 790 (footnote omitted).

Congress, likewise, has long understood and accepted that FPASA granted broad authority to the President. While Congress has revised the FPASA since 1949, including a complete recodification in 2002, none of those amendments modified or restricted the power being used by the President here.[8] "If a word or phrase has been . . . given a uniform interpretation by inferior courts . . . , a later version of that act perpetuating the wording is presumed to carry forward that interpretation." *Texas Dep't of Hous. & Cmty. Affairs v. Inclusive Communities Project, Inc.*, 576 U.S. 519, 536–37 (2015) (quoting A. Scalia & B. Garner, *Reading Law: The Interpretation of Legal Texts* 322 (2012)).

B. The Executive Order has a nexus with procurement efficiency required by the FPASA.

Presidential policies to direct government procurement need only be "reasonably related to the Procurement Act's purpose of ensuring efficiency and economy in government procurement." *Liberty Mut. Ins. Co.*, 639 F.2d at 170. Courts have "emphasized the necessary flexibility and 'broad-ranging authority'" that FPASA provides. *Chao*, 325 F.3d at 366. The standard is "lenient" and can be satisfied even when "the order might in fact increase procurement costs" in the short run. *Id.* at 366–67. Courts find a nexus even when "[t]he link may seem attenuated" and even if one can "advance an argument claiming opposite effects or no effects at all." *Id.* "[T]his close nexus requirement [] mean[s] little more than that President's explanation for how an Executive Order promotes efficiency and economy must be reasonable and rational." *Napolitano*, 648

[8] *See, e.g.*, Pub. L. 99-500, §101(m) [title VIII, §832], Oct. 18, 1986, 100 Stat. 1783-345; Pub. L. 99-591, §101(m) [title VIII, §832], Oct. 30, 1986, 100 Stat. 3341-345§ 101(f) [Title VI, § 611], Sept. 30, 1996, 110 Stat. 3009-355Pub.L. 107-217, 116 Stat. 1068 (Aug. 21, 2002).

F. Supp. 2d at 738 (one sentence explanation sufficient); *see also Reich*, 74 F.3d at 1333 ("The President's authority to pursue 'efficient and economic' procurement . . . certainly reach[es] beyond any narrow concept of efficiency and economy in procurement.") (collecting examples).

Executive Order 14,042 easily satisfies this lenient standard. The President explained in Section 1 of the EO:

> This order promotes economy and efficiency in Federal procurement by ensuring that the parties that contract with the Federal Government provide adequate COVID-19 safeguards to their workers performing on or in connection with a Federal Government contract . . . . These safeguards will decrease the spread of COVID-19, which will decrease worker absence, reduce labor costs, and improve the efficiency of contractors and subcontractors at sites where they are performing work for the Federal Government.

To anyone who has lived through the COVID-19 pandemic and its resulting economic turmoil, the nexus between reducing the spread of COVID-19 and economic efficiency is self-evident. While Plaintiffs may disagree with the President's policy or consider it unwise, the EO's explanation is sufficient to show the required nexus between the policy and promoting economy and efficiency. *Compare* EO, § 1 *with Chao*, 325 F.3d at 366–67 (holding sufficiently close nexus to efficient and economic procurement based on two sentences: "When workers are better informed of their rights, including their rights under the Federal labor laws, their productivity is enhanced. The availability of such a workforce from which the United States may draw facilitates the efficient and economical completion of its procurement contracts.").

EO 14,042 and the Acting OMB Director's related efficiency-and-economy determination clear this "lenient" standard with plenty of room to spare. *Chao*, 325 F.3d at 367. COVID-19 hobbled the economy for months and continues to disrupt American life. Federal procurement is no exception. The President, as the ultimate manager of procurement operations, determined that workplace safeguards aimed at preventing COVID-19's spread will "decrease worker absence,

reduce labor costs, and improve the efficiency of contractors and subcontractors at sites where they are performing work for the Federal Government." EO 14,042 § 1. Slowing COVID-19's spread promotes efficiency and economy because federal procurement—like any business endeavor—suffers when people contracting with the federal government get sick and miss work.

Plaintiffs rely on *Reich* to suggest that the President acted as a "regulator" when he issued the EO, and argue that if an EO touches on social policies other than procurement policy, then the EO is outside the permissible bounds of the FPASA. *Id.* (citing *Reich*, 74 F.3d 1322). But those quotes come from a section in *Reich* where was analyzing an entirely different issue—the preemptive effect of the National Labor Relations Act. *Reich*, 74 F.3d at 1334–35. Plaintiffs identify no similar statute that could have a preemptive effect here. Moreover, even though *Reich* ultimately found that EO conflicted with the NLRA, the opinion emphasized that it was *not* reaching any question about the scope of FPASA authority. *Id.* at 1332. At the same time it emphasized: "That is not to say that the President, in implementing the Procurement Act, may not draw upon any secondary policy views . . . that are directed beyond the immediate quality and price of goods and services purchased." *Id.*

While FPASA says nothing specific about vaccination or disease prevention, it also does not specifically authorize promoting urban renewal, promoting collective bargaining rights, conserving gasoline during an oil crisis, combating discrimination, verifying contractors' immigration status, or the other Presidential directives that have passed FPASA muster. *See, e.g.*, *City of Albuquerque*, 379 F.3d 901 (urban renewal); *Chao*, 325 F.3d 360 (collective bargaining rights); *Am. Fed'n of Gov't Emps., AFGE*, 669 F.2d 815 (energy conservation during an oil crisis); *Kahn*, 618 F.2d at 790 (noting multiple Presidents "prominent[ly]" used FPASA to impose "a series of anti-discrimination requirements for Government contractors"); *Napolitano*, 648 F. Supp.

2d at 729 (employee work eligibility). Rather, FPASA "emphasiz[es] the leadership role of the President in setting Government-wide procurement policy on matters common to all agencies" and expects "the President [to] play a direct and active part in supervising the Government's management functions." *Kahn*, 618 F.2d at 788.

Plaintiffs just ignore all these cases. Instead, Plaintiffs argue in broad terms that principles of federalism and their separate constitutional claims require a hard look at the nexus between the challenged action and the FPASA. Pls.' Mem. 21–25. Setting aside that Plaintiffs are unlikely to succeed on their constitutional claims, *infra* at X, Plaintiffs provide no compelling reason why this Court should radically depart from the way FPASA has been interpreted for more than 50 years.[9]

C. The President can delegate his policymaking authority to the OMB Director.

Plaintiffs also argue that the President and OMB Director's actions conflict with the FAR Council's statutory responsibility to "issue and maintain" the Federal Acquisition Regulation—a 2,000+-page regulation. Pls.' Mem. 19–20 (citing 41 U.S.C. § 1303(a)(1)). But the FAR Council's authority to issue regulations is not exclusive. Plaintiffs rely on Section 1303(a)(1) for their argument, but the very next subsection, Section 1303(a)(2)(A), permits agencies to prescribe "regulations essential to implement Government-wide policies and procedures." And, of course, the EO and the OMB Director's Determination set Government-wide procurement "policies" pursuant to 40 U.S.C. § 121(a), which authorizes the President to "prescribe policies."

[9] Pre-FPASA practice provides additional support. In 1941, President Franklin Roosevelt issued an executive order instructing that "[a]ll contracting agencies of the Government of the United States shall include in all defense contracts hereafter negotiated by them a provision obligating the contractor not to discriminate against any worker because of race, creed, color, or national origin." Executive Order 8802, 6 FR 3109 (June 27, 1941).

Section 3 of the EO recognizes these two sources of authority by (1) directing the FAR Council to revise the FAR, and (2) until the FAR is revised, directing agencies "to exercise any applicable authority" to implement the Government-wide policies and procedures described in the Executive Order and any subsequent OMB Determinations.

D. Plaintiffs' Notice and APA claims are not likely to succeed.

1. Plaintiffs' challenges to the OMB determination are not justiciable.

Plaintiffs challenge the OMB's initial determination, issued on September 24, 2021. As a threshold matter, Plaintiffs' APA challenge to that determination is moot because it has been expressly superseded by a new OMB Determination containing substantive changes. *See Akiachak Native Cmty. v. U.S. Dep't of Interior*, 827 F.3d 100, 113 (D.C. Cir. 2016) (noting the "well-settled principle of law" that "when an agency has rescinded and replaced a challenged regulation, litigation over the legality of the original regulation becomes moot.").

Further, neither the previous notice nor the operative OMB Determination is reviewable under the APA, because the OMB Determination is not an "agency action." "Because the President is not an 'agency' for purposes of the APA, presidential action is not subject to judicial review under that statute." *NRDC v. State*, 658 F. Supp. 2d 105, 109 (D.D.C. 2009) (citing *Franklin v. Massachusetts*, 505 U.S. 788, 800–01 (1992); *Dalton v. Specter*, 511 U.S. 462, 470 (1994)). The President delegated to the OMB Director, pursuant to 3 U.S.C. § 301, the authority to determine whether Guidance from the COVID Task Force "will promote economy and efficiency in Federal contracting." *See* EO 14,042, § 2(c). Section 301 authorizes the President to "to designate and empower the head of any department or agency in the executive branch, . . . to perform without approval, ratification, or other action by the President [] any func-

tion which is vested in the President by law," including the President's power to direct government contracting pursuant to 41 U.S.C. § 121(a). When exercising delegated authority, the official "stands in the President's shoes" and "cannot be subject to judicial review under the APA." *NRDC*, 658 F. Supp. 2d at 109 & n.5, 111; *see also Detroit Int'l Bridge Co. v. Canada*, 189 F. Supp. 3d 85, 100 (D.D.C. 2016), *aff'd*, 875 F.3d 1132 (D.C. Cir. 2017).

In arguing that OMB is an "agency" subject to APA review, Pls.' Mem. at 25, Plaintiffs ignore the distinction between the exercise of delegated Congressional power and Presidential authority. While OMB may sometimes act pursuant to Congressional dictates, such as in complying with the Natural Environmental Policy Act, *Sierra Club v. Andrus*, 581 F.2d 895, 897 (D.C. Cir. 1978), *rev'd,* 442 U.S. 347 (1979), or the Freedom of Information Act, *Meyer v. Bush*, 981 F.2d 1288, 1294 (D.C. Cir. 1993), it did not do so here. By acting under express Presidential delegation, OMB's determination falls outside the scope of APA review. *NRDC*, 658 F. Supp. 2d at 109 & n.5, 111.

Plaintiffs also fault the now-superseded OMB determination for not following the notice-and-comment requirements of 41 U.S.C. § 1707, Pls.' Mem. at 32–33, but Section 1707 also does not apply to exercises of Presidential authority such as the OMB determination. Section 1707 generally requires "the head of the agency" to publish a proposed "procurement policy, regulation, procedure, or form" in the Federal Register if the proposal "relates to the expenditure of appropriated funds" and either "has a significant effect beyond the internal operating procedures of the [issuing] agency" or "has a significant cost or administrative impact on contractors." 41 U.S.C. § 1707(a)(1), (b). But, as just explained, when the OMB Director exercises delegated presidential authority, she is not acting as "the head of [an] agency."

2. OMB's determination complies with the APA's substantive and procedural requirements.

Even if the Determination were subject to the APA, those claims would still fail because the Determination provides "a rational connection between the facts found and the choice made." *Dickson v. Sec'y of Def.*, 68 F.3d 1396, 1404–05 (D.C. Cir. 1995) (quoting *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983)). "Arbitrary and capricious is a highly deferential standard of review." *Adventist Health Sys./SunBelt, Inc. v. United States Dep't of Health & Hum. Servs.*, — F. 4th —,-No. 21-1589, 2021 WL 5170810, at *7 (8th Cir. Nov. 8, 2021). A court "simply ensures that the agency has acted within a zone of reasonableness and, in particular, has reasonably considered the relevant issues and reasonably explained the decision." *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021).

The OMB Determination is eminently reasonable. OMB approved the revised Task Force Guidance because it concluded that "[t]he safety protocols that are set forth" in the guidance "are meant to ensure that COVID-19 does not easily spread within the workplace, so that Federal contractor employees can continue to be productive." 86 Fed. Reg. at 63423. The requirement promotes economy and efficiency in federal contracting because decreasing worker absences reduces costs. As OMB explains, "[r]educing the number of infected people mechanically reduces transmission," and "evidence also indicates that vaccines also reduce transmission by people who contract 'breakthrough' infections." *Id.* at 63422. In conjunction with the other safety protocols proposed in the Workforce Guidance, the vaccine requirements will "prevent infection and illness and preserve the productivity" of federal contractors. *Id.*

OMB's Determination also explains that, in its judgment, requiring vaccination will not lead any meaningful number of workers to quit their jobs, thereby addressing Plaintiffs' concern about the "risk of negative economic impacts . . . from the prospect of large-scale resignations

and terminations of employees" and the ensuing "hardships to . . . citizens who lose their jobs." Pls.' Mem. at 28–29. OMB examined data from major private employers to see whether workers would leave their jobs instead of complying with vaccine requirements and concluded that there was "no systematic evidence that this has been a widespread phenomenon or that it would be likely to occur among employees of Federal contractors. In fact, the experience of private companies is to the contrary."[10] 86 Fed. Reg. at 63422 (citing evidence from Tyson Foods and United Airlines, among other companies). OMB's "predictive judgment," based on empirical evidence, is entitled to deference. *Rural Cellular Ass'n v. FCC*, 588 F.3d 1095, 1105 (D.C. Cir. 2009); *see also Newspaper Ass'n of Am. v. Postal Regulatory Comm'n*, 734 F.3d 1208, 1216 (D.C. Cir. 2013) ("When, as here, an agency is making 'predictive judgments about the likely economic effects of a rule,' we are particularly loath to second-guess its analysis.") (citation omitted).

Plaintiffs claim that the vaccine requirement's costs and disruptions to the States were not considered. Pls.' Mem. at 29. But OMB *did* consider the costs to covered contractors, including Plaintiffs, and determined that "[b]ecause vaccines are widely available for free, the cost of implementing a vaccine mandate is largely limited to administrative costs associated with distributing information about the mandate and tracking employees' vaccination status. Such costs are likely to be small." 86 Fed. Reg. 63422. As for "reliance interests," Pls.' Mem. at 30, Plaintiffs

[10] The article that Plaintiffs reference on page 15 of their brief, Chris Isidore & Virginia Langmaid, *72% of unvaccinated workers vow to quit if ordered to get vaccinated*, CNN (Oct. 28, 2021), https://perma.cc/7JMV-SULY, also includes the real-life data from these two companies and specifically notes that "[w]hat people say in a survey, and what they would [ultimately] do . . . can be two different things." *Id.*

fail to articulate any real harm from their "reliance" on the absence of a contractor vaccine requirement when enacting state laws. Further, EO 14,042 and the approved Task Force Guidance apply to new contracts or upcoming extensions to current contracts, which does a great deal to protect Plaintiffs' reliance interests on preexisting contract terms. OMB was entitled to approve guidance to manage federal operations and contracts on the basis of the data it considered, notwithstanding the presence of state and local measures that would be preempted for federal contracting purposes.

Plaintiffs' arguments that the underlying Task Force guidance is overinclusive, Pls.' Mem. at 29, do not render the OMB Determination arbitrary and capricious. The government need not "explore 'every alternative device and thought conceivable by the mind of man'" before making a decision. *Regents*, 140 S. Ct. at 1915 (quoting *Vt. Yankee Nuclear Power Corp. v. Nat. Res. Def. Council*, 435 U.S. 519, 551 (1978)); *see also Motor Vehicle Mrs. Ass'n*, 463 U.S.at 51 (declining to "require an agency to consider all policy alternatives in reaching [a] decision"). Further, OMB's approval of guidance that broadly construes the meaning of covered contractor employee was a policy choice, and while others may disagree, "[a] court cannot "substitute its judgment for that of the agency." *Adventist Health Sys./SunBelt,* , 2021 WL 5170810, at *7 (citation omitted).

Plaintiffs also argue that OMB's Determination was pretextual because it was actually about "federalizing the public-health response to the COVID-19 pandemic." Pls.' Mem. at 31. In support, they rely on an extra-record and inapposite statement made earlier in the pandemic by the White House Press Secretary and a retweet from a senior administration official about a different executive action with a broader scope and different purpose. Plaintiffs' attempts to rely on

material outside the administrative record as evidence of pretext, *see id.* at 26 n.19, should be rejected. As the Supreme Court has explained, when there is a "contemporaneous explanation" for an agency's decision, its validity "must . . . stand or fall on the propriety of that finding." *Camp v. Pitts*, 411 U.S. 138, 143 (1973).

Plaintiffs fail to establish that the OMB Determination and attendant explanation "is incongruent with what the record reveals about the agency's priorities and decisionmaking process." *Dep't of Comm. v. New York*, 139 S. Ct. 2551, 2575–76 (2019). As OMB reasonably concluded, slowing the spread of COVID-19 has an economically beneficial impact on federal operations, since federal workers are incurring significant labor costs from workers getting sick from COVID-19 and spreading it to others in the workplace. *See* 86 Fed. Reg. 63421–23. While such a policy may also have salutary public health effects, that result does not undermine the reasoning or legitimacy of OMB's decision. Further, even if the public-health effect was a background consideration, "a court may not reject an agency's stated reasons for acting simply because the agency might also have had other unstated reasons." *Dep't of Comm.*, 139 S. Ct. at 2573.

Nor can Plaintiffs succeed in claiming that the OMB Determination contains "impermissible *post hoc* rationalizations." Pls.' Mem. at 31. By explaining why the Task Force Guidance promoted government efficiency, OMB merely complied with EO 14,042 and the FPASA. And by superseding its old determination with a new Determination that further details why it initially approved the Task Force Guidance, OMB provided "a fuller explanation of the agency's reasoning *at the time of the agency action*," *Dep't of Homeland Sec. v. Regents of the Univ. of California*, 140 S. Ct. 1891, 1907–08 (2020) (emphasis in original) (quoting *Pension Benefit Guaranty*

Corporation v. LTV Corp., 496 U.S. 633, 654 (1990)), which is the opposite of post-hoc rationalization.

3. The OMB Determination also complied with any applicable procedural requirements under the Procurement Policy Act.

In any event, the new OMB Determination satisfies § 1707's procedural requirements. Section 1707 permits a proposal to become temporarily effective without publication and public comment if "the officer authorized to issue" the proposal finds that "urgent and compelling circumstances make compliance with [those] requirements impracticable." *Id.* § 1707(d)–(e). Here, the Acting OMB Director did just that by finding that the imminent threat of the COVID-19 pandemic and its impact on "worker absence," "labor costs," and "the efficiency of federal contracting" presented "[u]rgent and compelling circumstances justify[ing]" a waiver under § 1707(d). 86 Fed. Reg. at 63423–24. And consistent with § 1707(e), the Acting OMB Director "solicit[ed] comments on all subjects of" the OMB Determination, thus permitting the determination to become temporarily effective upon filing with the Federal Register on November 10, 2021 and mooting Plaintiffs' arguments on this score. *Id.* at 63423.

4. Challenges to the FAR Memo are likewise not likely to succeed.

The FAR Memo is also not subject to judicial review under the APA. To begin, Plaintiffs lack standing to challenge the FAR Memo because they (1) are not a party to a contract with the recommended clause, (2) have not identified any potential contracts that have the proposed provision, and (3) have not identified any injury that would be redressed by enjoining the FAR Memo. *See Transp. Workers Union of Am., AFL-CIO v. Transportation Sec. Admin.*, 492 F.3d 471, 477 (D.C. Cir. 2007) (no injury from guidance because "the change caused nothing" to happen to the claimant). The FAR Memo itself does not affect the authority of agencies to include a

COVID-19 safety clause in their contracts; agencies have authority to include a verbatim clause in contracts and solicitations even without the FAR Memo

The FAR Memo is also not a "final agency action." 5 U.S.C. § 704. The APA also provides review only of *final* agency action: a decision (1) that marks the "consummation of the agency's decisionmaking process" and (2) by which "rights or obligations have been determined, or from which legal consequences will flow." *Bennett v. Spear*, 520 U.S. 154, 177–78 (1997) (citation omitted). Neither prong is met here.

First, the FAR Memo is not final agency action because it is not the FAR Council's final word on the contract clause. The guidance was issued in accordance with the EO's instructions for the FAR to "take *initial* steps to implement" the contract clause described in the EO. EO 14,042 § 3(a) (emphasis added); *see also* FAR Memo at 1 ("The purpose of this memorandum is to provide agencies that award contracts under the . . . [FAR] with *initial* direction.") (emphasis added). The Memo suggests a clause for contracting officers to use in the interim, subject to agency- and contract-specific deviations to be developed by each agency. FAR Memo at 2. The conclusion of the policymaking process set forth in the EO—the FAR Council's amendment to the FAR by providing the contract clause "for inclusion in Federal procurement solicitation and contracts" subject to the EO—has yet to occur. EO 14,042 § 3(a); *see also* FAR Open Cases Report" at 2, available at https://www.acq.osd.mil/dpap/dars/opencases/farcasenum/far.pdf (indicating that on September 29, 2021, the FAR Council opened a case to implement EO 14,042 by drafting a proposed rule).

Second, the FAR Memo is not a decision from which "legal consequences will flow." *Bennett*, 520 U.S. at 177–78 (citation omitted). Plaintiffs cannot challenge guidance when they fail to show "any risk of future harm traceable to the . . . Guidance itself, as opposed to the

preexisting federal laws it describes." *Klayman v. President of United States*, 689 F. App'x 921, 924 (11th Cir. 2017). The Memo makes clear that the final decision from which legal consequences flow was EO 14,042—not the non-binding FAR guidance. FAR Memo ("The FAR Council has developed the attached clause pursuant to section 3(a) of the order to support agencies in meeting the applicability requirements and deadlines set forth in the order."). Alternatively, legal consequences would flow from the actual inclusion of a vaccine-requirement contract clause in a plaintiff's contract, which could be challenged before the agency board of contracting appeals or in the Court of Federal Claims, not *ex ante* in this Court.[7] 28 U.S.C. § 1346(a)(2); *id.* § 1491(a)(2).

Even if the FAR Memo was final agency action, Plaintiffs fail to challenge any specific aspect of the Memo as unreasonable. The FAR Council's guidance does nothing more than carry out the EO directive to "take initial steps to implement appropriate policy direction" for how agency acquisition offices can use the contract clause described in the EO. EO 14,042 § 3(a). In doing so, it merely reiterates the deadlines and requirements in the EO and provides a sample contract clause that incorporates the Task Force Guidance.

Section 1707's procedural notice requirements also do not apply to the FAR Memo because it is, at most, nonbinding guidance, and not "a procurement policy, regulation, procedure, or form" with "a significant effect beyond" the FAR Council's operating procedures. 41 U.S.C. § 1707(b). The FAR Council issued the memo to develop a template COVID-19 safety clause "to *support* agencies in meeting the applicability requirements and deadlines set forth in [EO 14,042]" and to "encourage[]" agencies to "exercise their authority" to temporarily deviate from the FAR by including similar clauses in their procurement contracts. FAR Memo at 2–3. The FAR Memo has no independent effect, however, and none of its guidance is operational unless

an agency chooses to incorporate it into a procurement contract. And the FAR Memo does not direct an agency to take any specific action, but instead encourages contracting officers to "follow the direction[s] … issued by their respect agencies" for how to utilize the memo's guidance. *Id.*

E. Plaintiffs' constitutional claims are meritless.

1. The challenged actions do not violate the Tenth Amendment.

Plaintiffs cannot succeed on a Tenth Amendment claim by simply invoking general maxims of federalism. The Tenth Amendment provides that "[t]he powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States respectively, or to the people." U.S. Const. amend. X. The powers specifically delegated to the federal government by the Constitution "are not powers that the Constitution 'reserved to the States.'" *United States v. Comstock*, 560 U.S. 126, 144 (2010); *accord New York v. United States*, 505 U.S. 144, 156 (1992) ("If a power is delegated to Congress in the Constitution, the Tenth Amendment expressly disclaims any reservation of that power to the States[.]"). Simply put: As long as federal action rests on a constitutionally delegated power, "there can be no violation of the Tenth Amendment." *United States v. Mikhel,* 889 F.3d 1003, 1024 (9th Cir. 2018) (citation omitted), *cert. denied*, 140 S. Ct. 157 (2019).

Where (as here) a federal statute is validly enacted under one of Congress's enumerated powers, and the Executive Branch exercises authority lawfully delegated under that statute, the Tenth Amendment is no bar to federal action. *See, e.g.*, *Wachovia Bank v. Watters*, 431 F.3d 556, 563 (6th Cir. 2005), *aff'd,* 550 U.S. 1 (2007). As explained above, *see supra* Argument I.A–C, EO 14,042 and the OMB Determination were issued pursuant to the President's authority under

the Procurement Act, a federal statute that was an evident exercise of Congress's power under the Spending Clause, *see infra* Argument I.E.4.

In addressing a Tenth Amendment claim, a court has "no license to employ freestanding conceptions of state sovereignty when measuring" federal authority under the Constitution. *Garcia v. San Antonio Metro. Transit Auth.*, 469 U.S. 528, 550 (1985). The only question under the Tenth Amendment is whether the federal government acts pursuant to one of its powers in the Constitution; if it does, a court "necessarily must also conclude that the [plaintiffs'] efforts to invoke abstract principles of federalism through the Tenth Amendment fail." *See, e.g.*, *Town of Johnston v. Fed. Hous. Fin. Agency*, 765 F.3d 80, 86 (1st Cir. 2014); *see also Garcia*, 469 U.S. at 549 ("States unquestionably do retain a significant measure of sovereign authority," but "only to the extent that the Constitution has not divested them of their original powers and transferred those powers to the Federal Government." (cleaned up)).

Plaintiffs also appear to suggest that a Tenth Amendment problem exists whenever federal action regulates subject matter that is also regulated by the states. *See* Pls.' Mem. 34 ("[t]he safety and the health of the people . . . are, in the first instance, for [the States] to guard and protect") (citation omitted)). But "[t]here is no general 'doctrine implied in the Federal Constitution that the two governments, national and state, are each to exercise its powers so as not to interfere with the free and full exercise of the powers of the other.'" *Maryland v. Wirtz*, 392 U.S. 183, 195 (1968), *overruled on other grounds by Nat'l League of Cities v. Usery*, 426 U.S. 833 (1976) (quoting *Case v. Bowles*, 327 U.S. 92, 101 (1946)). Indeed, it is axiomatic that the federal government does not "invade[] areas reserved to the States by the Tenth Amendment simply because it exercises *its* authority" under the Constitution, even "in a manner that *displaces* the States' exercise of their police powers." *Hodel v. Va. Surface Mining & Reclamation Ass'n*, 452 U.S. 264,

291 (1981) (emphasis added). Thus, "'the Federal Government, when acting within a delegated power, may override countervailing state interests,' whether those interests are labeled traditional, fundamental, or otherwise." *Brackeen v. Haaland*, 994 F.3d 249, 310 (5th Cir. 2021) (en banc) (op. of Dennis, J.) (quoting *Wirtz*, 392 U.S. at 195)), *petition for cert. filed*, No. 21-380 (U.S. Sept. 8, 2021).

Plaintiffs' argument also ignores that the terms of a federal contract are an exclusively *federal* concern. Under the doctrine of intergovernmental immunity, a federal contractor is immune from conflicting state laws and regulations even when those state laws are purportedly based on state police power. The doctrine arises from the Supremacy Clause and bars state regulations that "retard, impede, burden, or in any manner control the operations of the constitutional laws enacted by [C]ongress to carry into effect the powers vested in the national government." *M'Culloch v. Maryland*, 17 U.S. (4 Wheat.) 316, 317 (1819). "For purposes of intergovernmental immunity, federal contractors are treated the same as the federal government itself." *U.S. v. Cal.*, 921 F.3d 865, 882 n.7 (9th Cir. 2019). Courts regularly conclude that government contractors are immune from conflicting state laws, even when those laws are based on state power to regulate health and safety. *See Boeing Co. v. Movassaghi*, 768 F.3d 832, 840 (9th Cir. 2014); *GEO Grp., Inc. v. City of Tacoma*, No. 3:18-cv-05233, 2019 WL 5963112, at *5 (W.D. Wash. Nov. 13, 2019), *appeal dismissed*, 2020 WL 1249388 (9th Cir. Jan. 21, 2020). The Federal Government may contract with whom it likes under whatever terms it pleases without interference from states.

2. Contracts for services do not commandeer state officials.

Plaintiffs argue that is unconstitutional for a contract between a State and Federal Government to include a clause that compels a State to perform according to the terms of the contract—because requiring compliance would "commandeer" State officials. Pls.' Mem. at 35–36 (citing *Printz v. United States*, 521 U.S. 898 (1997)). The case Plaintiffs rely on for this remarkable position, *Printz*, held no such thing. In *Printz*, Congress directed state officials—who had not voluntarily entered into any contract—to perform certain duties related to firearms background checks. *Printz*, 521 at 903 –04. Plaintiffs ignored that *Printz* explained that if Congress had *contracted* with state officials, rather than merely commanding them, then there would have been no constitutional issue. *Id.* at 936 (O'Connor, J., concurring) ("Congress is also free to amend the interim program to provide for its continuance on a contractual basis with the States if it wishes, as it does with a number of other federal programs."); *see id.* at 916 (noting historical practice of contracting with state officials). Indeed, adopting Plaintiffs' view of the anti-commandeering doctrine would render all contracts between Federal and State governments unconstitutional.

3. Federal contracts do not violate the Commerce Clause.

Plaintiffs next claim that imposing requirements on its federal contracting workforce violates the Commerce Clause. Pls.' Mem. at 36 (citing *NFIB v. Sebelius*, 567 U.S. 519, 555 (2012)). But *NFIB* involved a challenge to a general mandate requiring most Americans to purchase health insurance, and the Court held that requirement exceeded Congress's power to regulate commerce. But here the government is not using its Commerce Clause authority to regulate anything. Instead, the government has set conditions on who the government does business with—something private-sector business leaders do all the time. *Cf. Arbitraje Casa de Cambio,*

S.A. de CV. v. United States, 79 Fed. Cl. 235, 240–41 (Fed. Cl. 2007) (noting that when contracting with other parties, "the sovereign steps off the throne and engages . . . as private parties, individuals or corporations also engage in among themselves"). "Like private individuals and businesses, the Government enjoys the unrestricted power to produce its own supplies, to determine those with whom it will deal, and to fix the terms and conditions upon which it will make needed purchases." *Perkins v. Lukens Steel Co.*, 310 U.S. 113, 127 (1940). "Those wishing to do business with the Government must meet the Government's terms; others need not." *Am. Fed'n of Lab. & Cong. of Indus. Organizations v. Kahn*, 618 F.2d 784, 794 (D.C. Cir. 1979) (en banc). The policies at issue in this case are not a generally applicable regulations, and they do not implicate the Commerce Clause.

4. The challenged actions do not violate the Spending Clause.

Plaintiffs also claim that EO 14,042 and its implementing guidance exceed a limitation imposed on the federal government's spending power because the "mandate fails to 'unambiguously' establish the contract terms." Pls.' Mem. at 35 (quoting *Pennhurst State Sch. & Hosp. v. Halderman*, 451 U.S. 1, 17 (1981)). Plaintiffs also claim that the mandate exceeds Congress's Spending Clause power because it "is not 'related to the federal interest in particular national projects or programs.'" *Id.* (quoting *Van Whye v. Reisch*, 581 F.3d 693, 650 (8th Cir. 2009)).

These limits on Congress's authority to condition grants of federal funding do not apply to federal contracts. Plaintiffs cite no case where a court has found federal contract obligations invalid under *Pennhurst*'s clarity requirement or *Van Whye*'s federal interest requirement.[11] And

[11] The President has already determined that including the COVID-19 safety clause is in the federal interest, *see supra*, Argument I. B., and the OMB Director's Determination provides additional details, *supra* Argument I.D.

for good reason: adopting Plaintiffs' position would make simple imprecisions in federal procurement contracts matters of constitutional magnitude. As the Supreme Court has explained, even "the consequences of imprecision" in spending legislation "are not constitutionally severe" when the government "is acting as patron rather than as sovereign." *See Nat'l Endowment for the Arts v. Finley*, 524 U.S. 569, 589 (1998). The same is true when the government procures property or services in the same manner "as private parties, individuals or corporations also engage in among themselves." *See Arbitraje Casa de Cambio, S.A. de CV.*, 79 Fed. Cl at 240–41 (Fed. Cl. 2007) (citation omitted).

At any rate, EO 14,042 and its implementing guidance unambiguously put contractors on notice that compliance with OMB-approved Task Force Guidance is an obligation under a covered contract. *Pennhurst* requires nothing more. *See Benning v. Georgia*, 391 F.3d 1299, 1307 (11th Cir. 2004). The Court in *Pennhurst* was concerned with a federal grant program that "was unclear as to whether the states incurred *any* obligations *at all* by accepting federal funds." *See id.* (emphasis added); *accord Ky., Dep't of Hum. Resources v. Donovan*, 704 F.2d 288, 299 n.17 (6th Cir. 1983). Here, however, EO 14,042 ensures that "the *existence* of the condition itself" will be "explicitly obvious" to federal contractors by directing agencies to incorporate (to the extent permitted by law) a COVID-19 safety clause into a contract before obligating a contractor's compliance. *See Benning*, 391 F.3d at 1307 (emphasis added) (quoting *Mayweathers v. Newland*, 314 F.3d 1062, 1067 (9th Cir. 2002)). For each covered contract, a clause can only be incorporated upon the mutual agreement of the parties. Thus, because the challenged actions ensure that the "*intention to impose a condition* is expressed clearly" in a covered contract, *see Mayweathers*, 314 F.3d at 1067, a state will be capable of making "an informed," voluntary decision whether to accept the attendant obligations of contracting with the federal government, *see*

Pennhurst, 451 U.S. at 25; *see also id.* at 17 (conditions must be imposed clearly so a state is not "unaware of the conditions" or "unable to ascertain what is expected of [them]").

Furthermore, Plaintiffs stake their entire claim on the fact that agencies are encouraged under the FAR Memo to include a provision requiring a contractor to "comply with all guidance . . . as amended during the performance' of the contract 'published by the . . . Task Force'"). *See* Pls.' Mem. at 35. But the Supreme Court has not required exactitude when conditioning federal funding. *See, e.g.*, *Bennett v. Ky. Dep't of Educ.*, 470 U.S. 656, 669 (1985) ("[T]he Federal Government simply could not prospectively resolve every possible ambiguity concerning particular applications of [a grant program's] requirements …."). Indeed, "the Supreme Court has held that conditions may be 'largely indeterminate,'" and yet constitutionally permissible, "so long as the statute 'provid[es] clear notice to the States that they, by accepting funds under [federal law], would indeed be obligated to comply with [the conditions]." *Mayweathers*, 314 F.3d at 1067 (quoting *Pennhurst*, 451 U.S. at 24–25). Federal contractors are capable of making informed, voluntary decisions to accept an obligation to comply with periodically updated guidelines. *See Donovan*, 704 F.2d at 299 ("Thus, the state voluntarily accepts the Secretary's power to alter the program and require compliance.").

5. The challenged actions do not violate the nondelegation doctrine.

Plaintiffs contend that the Procurement Act violates the Constitution's nondelegation doctrine if it authorizes the President to issue EO 14,042. *See* Pls.' Mem. at 22–23. To the contrary, the Procurement Act's delegation of authority fits comfortably within the bounds of constitutionally permissible delegations. Congress may lawfully delegate decision-making authority so long as it "lay[s] down by legislative act an intelligible principle to which the person or body au-

thorized to [act] is directed to conform." *Mistretta v. United States*, 488 U.S. 361, 372 (1989) (citation omitted). A delegation is "constitutionally sufficient if Congress clearly delineates [1] the general policy, [2] the public agency which is to apply it, and [3] the boundaries of this delegated authority." *Id.* at 372–73 (citation omitted); *accord Gundy v. United States*, 139 S. Ct. 2116, 2129 (2019) (plurality op.) ("[A] delegation is permissible if Congress has made clear to the delegee 'the general policy' he must pursue and the 'boundaries of his authority.'" (cleaned up)).

The intelligible-principle standard is so deferential that the Supreme Court has "almost never felt qualified to second-guess Congress regarding the permissible degree of policy judgment that can be left to those executing or applying the law." *Whitman v. Am. Trucking Ass'ns*, 531 U.S. 457, 474–75 (2001) (quoting *Mistretta*, 488 U.S at 416 (Scalia, J., dissenting)). In fact, the Supreme Court has struck down congressional delegations only twice in United States history—both in 1935—and only because "Congress had failed to articulate *any* policy or standard" to confine discretion. *Gundy*, 139 S. Ct. at 2129. Over the last eighty years, the Court "has countenanced as intelligible seemingly vague principles in statutory text such as whether something would 'unduly or unnecessarily complicate,' … be 'generally fair and equitable,' in the 'public interest,' … [or] authoriz[es] the recovery of excessive profits." *In re Nat'l Sec. Agency Telecomms. Recs. Litig.*, 671 F.3d 881, 896 (9th Cir. 2011) (citing multiple cases); *see also, e.g.*, *Indus. Union Dep't, AFL-CIO v. Am. Petroleum Inst.*, 448 U.S. 607, 646 (1980) (upholding delegation to determine what constituted a "safe" place of employment); *Gundy*, 139 S. Ct. at 2129 (noting that the Supreme Court has, on multiple occasions, "approved delegations to various agencies to regulate in the 'public interest'" (citing *Nat'l Broad. Co. v. United States*, 319 U.S. 190, 216 (1943), and *N.Y. Cent. Secs. Corp. v. United States*, 287 U.S. 12, 24 (1932))); *id.*

at 2130–31 (Alito, J., concurring in the judgment) ("[S]ince 1935, the Court has uniformly rejected nondelegation arguments and has upheld provisions that authorized agencies to adopt important rules pursuant to extraordinarily capacious standards.").

In light of this longstanding precedent, the statute at issue here reflects an intelligible principle that falls well within permissible bounds. This is not a regulation that binds the general public; it only applies to contractors. The Procurement Act sets forth a general policy—the promotion of economy and efficiency in the federal government's procurement of property and services, *see* 40 U.S.C. § 101—and authorizes the President to issue orders designed to further those specific statutory goals in that narrow, definable context, *see id.* § 121(a). The statute's criteria thus establish a clear boundary for the President's actions, and compares favorably to other congressional delegations that have been sustained against challenges under the nondelegation doctrine. *See, e.g.*, *Whitman*, 531 U.S. at 474–75 (listing cases). Several courts have already held that the Procurement Act's delegation of authority to the President is valid. *See Kahn*, 618 F.2d at 785–86, 793 n.51 ("[The Procurement Act] requires the President to make procurement policy decisions based on considerations of economy and efficiency. Although broad, this standard can be applied generally to the President's actions to determine whether those actions are within the legislative delegation."); *City of Albuquerque*, 379 F.3d at 914–15 (finding the Procurement Act's limit that the President "establish 'an economical and efficient system for . . . the procurement and supply' of property" provided an "'intelligible principle' to guide the exercise" of the "relatively broad delegation of authority" in the statute (citations omitted).

Plaintiffs cite no authority to the contrary. Instead, they largely reiterate their statutory objections, maintaining that EO 14,042 "has no basis in the text of" the Procurement Act, but if it did, the statute would be too "broad." *See* Pls.' Mem. 23. But that is not the standard. "Congress

does not violate the Constitution merely because it legislates in broad terms, leaving a certain degree of discretion to executive or judicial actors." *Touby v. United States*, 500 U.S. 160, 165 (1991). As the Supreme Court has acknowledged, "Congress simply [could not] do its job absent an ability to delegate power under broad general directives." *Mistretta*, 488 U.S. at 372. In sum, only if this Court "could say that there is an *absence* of standards for the guidance of the [President's] action, so that it would be impossible in a proper proceeding to ascertain whether the will of Congress has been obeyed, would [the Court] be justified in overriding [Congress's] choice of means for effecting its declared purpose" in the Procurement Act. *See Yakus v. United States*, 321 U.S. 414, 426 (1944) (emphasis added). That is not the case here.

II. Plaintiffs do not face irreparable harm.

Plaintiffs are also not entitled to a preliminary injunction because they have failed to show a likelihood of irreparable harm. That showing must demonstrate that irreparable harm is *likely*, not merely possible, *Winter*, 555 U.S. at 20. "To succeed in demonstrating a threat of irreparable harm, 'a party must show that the harm is certain and great and of such imminence that there is a clear and present need for equitable relief.'" *Roudachevski v. All-Am. Care Centers, Inc.*, 648 F.3d 701, 706 (8th Cir. 2011) (citation omitted). Plaintiffs have not carried this burden here.

First, Plaintiffs have not alleged any irreparable harm from their position as federal contractors. Because EO 14,042 applies only to certain types of contracts entered into or extended on or after October 15, 2021, Plaintiffs cannot rely on ongoing contracts of indeterminate value that are not imminently up for renewal or extension to support irreparable harm. Here, Plaintiffs submit a bevy of declarations in support of their irreparable, but they miss the mark. Many of the

declarations (1) claim in general terms that Plaintiffs contract with the federal government,[12] (2) allege potential harm to contracts far in the future,[13] and (3) describe contracts either for an unspecified amount of money or that are affirmatively below the simplified acquisition threshold amount of $250,000 and thus not subject to the EO.[14] EO 14,042 § 5(a).

Other declarations describe federal agency attempts to seek bilateral modifications to include the safety-protocol clause into existing contracts.[15] While agencies are "strongly encouraged" under EO 14,042 to incorporate the Task Force's COVID-19 safety protocols into "existing contracts," they can only do so "to the extent permitted by law." *See* EO 14,042, § 6(c). Most of the contracts that Plaintiffs identify can be amended only upon the mutual, written

[12] Decl. of Ryan Rapp, ECF No 9-6; Decl. of Jason Jackson, ECF No. 9-13; Decl. of Marcia Mahaney, ECF No. 9-14.

[13] Decl. of Andrew Armacast, ECF No. 9-10 ¶¶ 3–4 (describing contracts set to expire in 2023 and 2025); Decl. of Tara Evans, ECF No. 9-11 ¶ 8 (describing contracts up for renewal in August 2022 and in 2023).

[14] Decl. of David Scanlan ¶ 7, ECF No. 9-9 (describing a contract potentially up for renewal on December 31, 2021 and others expiring later all worth less than $250,000); Evans Decl. ¶¶ 7, 11 (describing contracts up for renewal at the end of the year worth less than $250,000); Decl. of Dru Buntin ¶ 3, ECF No. 9-15 (describing three contracts worth unspecified amounts that are set to "expire on December 31, 2021," without establishing whether they are up for renewal or extension).

[15] *E.g.*, Decl. of Kraig Paulsen, ECF No. 9-7; Decl. of Patrick Hackley, ECF No. 9-8; Decl. of Karen Pat Pitney, ECF No. 9-12.

agreement of the parties. But these bilateral modifications are not required by the EO and are effective only upon both parties' approval.[16] Being asked to change a contract term, and voluntarily agreeing to the change, is not irreparable harm.[17]

In any event, were a federal agency to assert that EO 14,042 requires the insertion of a clause into an existing contract, Plaintiffs could dispute the existence of such a requirement by making a claim to the contracting officer under the Contract Disputes Act. The CDA "applies to any express or implied contract entered into by an executive agency for the procurement of property, services, construction, repair, or the disposal of personal property." *Anselma Crossing, L.P. v. USPS*, 637 F.3d, 238, 240 (3d Cir. 2011); *see* 28 U.S.C. § 1491(a)(2). It requires that a contractor present for a contracting officer's decision any claim "relating to a contract," 41 U.S.C.A.

[16] Plaintiffs identify one contract they claim was unilaterally modified by the Department of Energy (DOE), with Iowa State University (ISU). Decl. of Kraig Paulsen, ECF No. 9-7. As DOE confirms, it rescinded the unilateral modification of the contract to include the DOE's FAR Deviation Clause, though the agency ultimately unilaterally included another Task Force Guidance order in accordance with a DOE order. *See* Decl. of Cody Benjamin, Ex. 2 ¶ 5–7. To the extent ISU shows irreparable harm from the EO, it is the only entity to do so, any preliminary injunctive relief should be limited to this contract. *Gill v. Whitford*, 138 S. Ct. 1916, 1933–34 (2018) ("[a] plaintiff's remedy must be tailored to redress the plaintiff's particular injury.").

[17] Plaintiffs also claim that the General Services Administration (GSA) is exerting pressure on Missouri to enter into a bilateral modification for three contracts. Decl. of Dru Buntin ¶ 3, ECF No. 9-15. But that is not the case either; the allegedly coercive language the Buntin Declaration quotes without support does not even apply to the three contracts described in that declaration. They are not the types of contracts subject to the "interim measures" GSA explained it would take, *see* Gen. Serv. Admin., FAR Class Deviation - Implementation of Executive Order 14042, Ensuring Adequate COVID Safety Protocols for Federal Contractors, *available at* https://www.gsa.gov/cdnstatic/Class%20Deviation%20CD-2021-13_0.pdf (last accessed Nov. 18, 2021) (describing interim measures to be taken as to Indefinite Delivery Indefinite Quantity contracts); Decl. of Erica Hoffman ¶ 7, Ex. 3 ("The GSA-Missouri DNR Contracts are not . . . IDIQ contracts or Federal Supply Schedule contracts."). Moreover, the contracts are also all under the "simplified acquisition threshold" amount of $250,000 and thus outside the scope of the EO. *Id.* ¶¶ 9–10; *see also* EO 14,042 § 5(b)(iii).

§ 7103, with the decision reviewable by the Court of Federal Claims or a board of contract appeals. Similarly, if Plaintiffs were to contend that a federal government solicitation for a new contract included a COVID-19 related clause not mandated by law, 28 U.S.C. § 1491(b)(1) provides the Court of Federal Claims with jurisdiction to "render judgment on an action by an interested party objecting to a solicitation by a Federal agency for bids or proposals for a proposed contract or to a proposed award or the award of a contract or any alleged violation of statute or regulation in connection with a procurement or a proposed procurement." For these separate and independent reasons, Plaintiffs have failed to carry their burden to demonstrate irreparable harm. *United States of America v. Jefferson Cnty.*, 720 F.2d 1511 (11th Cir. 1983) ("The possibility [that] adequate compensatory or other corrective relief will be available at a later date, in the ordinary course of litigation, weighs heavily against a claim of irreparable harm.") (quoting *Samsung v. Murray*, 415 U.S. 61, 90 (1974).

Second, Plaintiffs also claim that EO 14,042 and its implementing guidance will harm them by causing "direct sovereign injuries." Pls.' Mem. at 37. But this claim simply reiterates Plaintiffs' doctrinally barren view of the Tenth Amendment. Again, it is black-letter law that the federal government does not "invade[]" areas of state sovereignty "simply because it exercises *its* authority" in a way that preempts conflicting state laws, even "in a manner that displaces the States' exercise of their police powers." *Hodel*, 452 U.S. at 291 (emphasis added). Here, EO 14,042 and the OMB Determination, and the FAR Memo were issued pursuant to delegated authority under the Procurement Act. *See supra* § I.C. And as federal law, these actions preempt conflicting state laws by simple operation of the Supremacy Clause, and nothing in the text or

structure of the Constitution entitles Plaintiffs to enact or enforce laws and policies that conflict with federal law.[18]

Third, Plaintiffs invoke the *parens patriae* doctrine "to prevent the manifest irreparable injury to their millions of citizens." Pls.' Mem. at 40. Although a state may have standing to vindicate its own injuries, *see Massachusetts v. EPA*, 549 U.S. 497, 520 n.17 (2007), "a state does not have standing as *parens patriae* to bring an action against the Federal government." *Alfred L. Snapp & Son, Inc. v. Puerto Rico*, 458 U.S. 592, 610 n.16 (1982); *see also Iowa ex rel. Miller v.* Block, 771 F.2d 347, 355 (8th Cir. 1985) ("[W]e cannot allow the State to proceed as parens patriae in this case" against the federal government. "To do so would intrude on the sovereignty of the federal government and ignore important considerations of our federalist system."). Plaintiffs' reliance on the *parens patraie* doctrine as a basis for irreparable injury is therefore misplaced.

III. The equities and the public interest weigh against injunctive relief.

The third and fourth requirements for issuance of a preliminary injunction—the balance of harms and whether the requested injunction will disserve the public interest—"merge when the Government is the opposing party." *Nken v. Holder*, 556 U.S. 418, 435 (2009). Here, these considerations tilt decisively in the Defendants' favor.

[18] Plaintiffs' reliance on *Maryland v. King*, 567 U.S. 1301 (2012) (Roberts, C.J., in chambers), and *Abbott v. Perez*, 138 S. Ct. 2305 (2018), is misplaced. Neither support the theory that states suffer irreparable injury whenever the federal government "prevent[s]" them "from effectuating" their own laws. *See* Pls.' Mem. at 39 (citation omitted). If such a rule existed, a state would suffer irreparable harm per se from all federal laws with preemptive effect. Instead, each case held that a state defendant established irreparable harm sufficient to grant a stay of a lower court's injunction barring the state from enforcing a challenged state law—a scenario not at issue here.

First, enjoining EO 14,042 would harm the public interest by hampering the efficiency of the contractors on which the federal government relies. The COVID-19 pandemic has interfered with numerous aspects of the government's work, *e.g.*, by forcing office closures; interfering with employees' access to paper-based or sensitive records; limiting official travel; and causing staffing shortages. *See generally* Pandemic Response Accountability Committee, Top Challenges Facing Federal Agencies (June 2020), https://perma.cc/GGF4-F4FV. These disruptions have affected the work of federal employees and federal contractors alike. Requiring federal covered contractor employees to become fully vaccinated against COVID-19, with exceptions only as required by law, reduces disruptions caused by worker absences associated with illness or exposure to the virus, generating meaningful gains in contracting efficiency. Enjoining EO 14,042 would prevent these gains and would likely interfere with the government's ability to resume normal, pre-pandemic operations.

Second, enjoining EO 14,042 would harm the public interest in slowing the spread of COVID-19 among millions of federal contractors and the members of the public with whom they interact. As the Supreme Court has recognized, "[s]temming the spread of COVID-19 is unquestionably a compelling interest." *Roman Catholic Diocese of Brooklyn v. Cuomo*, 141 S. Ct. 63, 67 (2020). Accordingly, numerous courts reviewing "executive action designed to slow the spread of COVID-19" have concluded that "[t]he public interest in protecting human life—particularly in the face of a global and unpredictable pandemic—would not be served by" an injunction. *Tigges v. Northam*, 473 F. Supp. 3d 559, 573–74 (E.D. Va. 2020); *see also, e.g.*, *Am.'s Frontline Drs. v. Wilcox*, No. EDCV 21-1243, 2021 WL 4546923, at *8 (C.D. Cal. July 30, 2021); *Valdez v. Grisham*, ---F. Supp. 3d---, 2021 WL 4145746, at *13 (D.N.M. Sept. 13, 2021), *appeal filed*, No. 21-2105 (10th Cir. Sept. 15, 2021), *Harris v. Univ. of Mass., Lowell*, ---F.

Supp. 3d---, 2021 WL 3848012, at *8 (D. Mass. Aug. 27, 2021), *appeal filed*, No. 21-1770 (1st Cir. Sept. 28, 2021), *Williams v. Brown*, ---F. Supp. 3d---, 2021 WL 4894264, at *10-11 (D. Or. Oct. 19, 2021); *Wise v. Inslee*, No. 2:21-cv-0288, 2021 WL 4951571, at *6 (E.D. Wash. Oct. 25, 2021), *Mass. Corr. Officers Federated Union v. Baker*, ---F. Supp. 3d---, 2021 WL 4822154, at *7-8 (D. Mass. Oct. 15, 2021), *Johnson v. Brown*, --- F. Sup. 3d---, 2021 WL 4846060, at *26-27 (D. Or. Oct. 18, 2021); *TJM 64, Inc. v. Harris*, 475 F. Supp. 3d 828, 840–41 (W.D. Tenn. 2020); *Talleywhacker, Inc. v. Cooper*, 465 F. Supp. 3d 523, 543 (E.D.N.C. 2020); *Brnovich v. Biden,* 2:21-cv-01568 (D. Az.) (denying preliminary injunction regarding federal government contractor vaccine requirement).

Moreover, granting the requested relief is not needed to preserve the status quo—existing contracts generally do not change without bilateral agreement of the parties. And granting the requested injunction would upend the status quo by (1) preventing further implementation of EO 14,042, which has been in effect for over two months; and (2) interfering with the federal government's ability to determine the terms on which it will enter into contracts. *See, e.g.*, *Nken*, 556 U.S. at 428–29 (explaining that enjoining a government policy is an act of "judicial intervention" that "*alter[s]* the legal status quo"). Further, granting the relief would allow challengers to obtain a preliminary injunction against *any* new government policy, in order to maintain the prior "status quo" until a decision on the merits. *But see Winter*, 555 U.S. at 24 ("A preliminary injunction is an extraordinary remedy never awarded as of right."); *Brown v. Gilmore*, 533 U.S. 1301, 1303 (2001) (Rehnquist, C.J., in chambers) (explaining that "an injunction against the enforcement of a presumptively valid" enactment should only be granted in extraordinary circumstances).

Against these weighty and substantial federal interests, Plaintiffs advance only vague notions of federalism. Setting aside that Plaintiffs' specific federalism claims are meritless for the

reasons stated above, the public interest in "federalism" actually cuts against Plaintiffs' position. Plaintiff States overstep their federalist bounds by seeking to interfere with the federal government's ability to enter into contracts on its own terms. And by seeking a nationwide injunction, Plaintiff States are trying reach beyond their borders to interfere with contracts the federal government has with their sister States and private parties completely unrelated to Plaintiffs. Plaintiffs unquestionably disagree with the policy determinations that undergird EO 14,042, but they do not have the right or authority to control federal contracting policy across America.

In sum, granting the pending motion would harm the public interest far more than denying the motion would harm Plaintiffs, and the motion should therefore be denied.

IV. In all events, this Court should not enter nationwide relief.

Although preliminary relief is unjustified here, at a minimum, any such relief should be no broader than necessary to redress Plaintiffs' alleged injuries. Because this Court's "constitutionally prescribed role is to vindicate the individual rights of the people appearing before it," "[a] plaintiff's remedy must be tailored to redress the plaintiff's particular injury." *Gill v. Whitford*, 138 S. Ct. 1916, 1933–34 (2018) (citation omitted). Nationwide injunctions are inappropriate and "take a toll on the federal court system—preventing legal questions from percolating through the federal courts, encouraging forum shopping, and making every case a national emergency for the courts and for the Executive Branch." *Trump v. Hawaii*, 138 S. Ct. 2392, 2425 (2018) (Thomas, J., concurring). EO 14,042 and its implementing guidance have been challenged in numerous other cases, underscoring why this Court should not attempt to decide its legality for all parties. *See e.g.*, *Brnovich v. Biden,* 2:21-cv-01568 (D. Az.) (denying preliminary injunction regarding government contractor vaccine mandate); *Smith v. Biden*, No. 1:21-cv-19457, 2021 WL 5195688, at *8 (D.N.J. Nov. 8, 2021) (same); *Texas v. Biden,* 3:21-cv-

00309; *Georgia v. Biden*, 1:21-cv-163 (S.D. Ga.); *Missouri v. Biden*, 4:21-cv-1300 (E.D. Mo.); *Oklahoma v. Biden*, 5:21-cv-01069 (W.D. Okla.); *Louisiana v. Biden*, 1:21-cv-3867 (W.D. La.); *Hollis v. Biden*, 1:21-cv-163 (N.D. Miss.); *Navy Seal 1 v. Biden*, No. 21-2429 (M.D. Fla.).

Here, any relief should be limited to harmed contracts identified in Plaintiffs' motion. And any relief should block enforcement—but not inclusion—of a COVID-19 safety clause. Allowing COVID-19 safety clauses to be included but not enforced during the pendency of this litigation would mean that: contractors within its scope would not have to require their employees to be vaccinated. But if EO 14,042 and its implementing guidance are ultimately upheld, the policy can be put into effect without further delay.[19]

CONCLUSION

For the foregoing reasons, Plaintiffs' motion for a preliminary injunction should be denied.

DATED: November 18, 2021

Respectfully submitted,

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[19] Allowing COVID safety clauses to be included but not enforced will not precipitate lay-offs or a rush to vaccination if the injunction is dissolved. Covered contractor employers have flexibility to "determine the appropriate means of enforcement" and to craft "polic[ies] that encourage[] compliance." Safer Federal Workforce, Federal Contractor FAQs, Compliance, https://perma.cc/RGR9-ZTES. In other words, covered contractors would not need to immediately fire unvaccinated employees once the injunction is dissolved. Rather, covered contractors should provide for a "period of counseling and education, followed by additional disciplinary measures if necessary," before terminating an employee or putting them on leave. *Id.*

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Exhibit 1

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA

JANE DOE #1, et al. Plaintiffs, v. LLOYD AUSTIN, III, in his official capacity as Secretary of Defense, et al. Defendants.	)	Case No. 1:21-cv-01211-AW-HTC

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-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

[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.

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.

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]

[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.

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. 7, n.13 (October 20, 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 12 through 15 years old; for a third dose in certain populations; and for a "booster" dose in certain circumstances.

9. Additionally, FDA determined that "[t]he licensed vaccine has the same formulation as the EUA-authorized vaccine and the products can be used interchangeably to provide the vaccination series without presenting any safety or effectiveness concerns." Letter to Pfizer, Inc. reissuing EUA authorization for Covid-19 vaccine, p. 2, n.8 (August 23, 2021), attached as Exhibit C. 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 individuals who had received Pfizer-BioNTech for the first dose were not authorized to receive Comirnaty for the second dose, or vice versa.

10. 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*).

11. 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.

12. 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] Both BLA and EUA manufacturing of this vaccine must adhere to FDA's current good manufacturing practice regulations, which are designed to ensure that the products meet specified standards of 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); EUA Reauthorization at 11 (Sept. 22, 2021), available at https://www.fda.gov/media/150386/download.

13. 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

[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 11-12.

[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. 6-8 (Sept. 22, 2021), available at https://www.fda.gov/media/144413/download.

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 other BLA-compliant lots are used for the approved indication. FDA worked with the Applicant to develop a Dear Healthcare Provider letter and website to identify those lots. Summary Basis for Regulatory Action – Comirnaty ("SBRA"), p. 27 (Aug. 23, 2021), attached as Exhibit D. 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 (Sept. 22, 2021), available at https://www.fda.gov/media/144414/download.

14. 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 D, 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.

15. 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.

16. 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 D, 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 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.

17. 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 D, 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

[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 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 availability of effective treatment also encourages participation in clinical trials. Overall, the decision regarding when to "unblind" a clinical trial involves a delicate balance of competing priorities.

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 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 E. 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).

18. 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 D, SBRA at 15. Safety data from the study was included in the BLA for Comirnaty and supported selection of the

[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 Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines (fda.gov) (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.

final vaccine candidate and dose level. *Id*. at 21. Although FDA did not refer the BLA to its 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.

19. 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).

20. Based on the data from the two clinical studies, FDA determined 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 D, 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).

21. 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 D, SBRA at 29-30.

22. 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 SARSCoV-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 19, 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 21 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 at 7-8 (August 23, 2021), attached as Exhibit G.

23. 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.

24. 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 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.

25. I have reviewed the Declaration of Jane Ruby submitted in this matter. ECF No. 1-18. Although I have not attempted to exhaustively analyze her conclusions, the declaration is rife with error and appears to reflect a lack of basic knowledge of the field. For example, I disagree with Ms. Ruby's assertion that the phased unblinding of participants in C4591001 renders the data from the trial "completely compromised." *See id.* at ¶12. As explained above in paragraph 17 and in FDA's Clinical Review at 26, referenced in Paragraph 19 above, that participants initially assigned to the placebo arm of the study were unblinded in phases in accordance with the protocol does not invalidate the data generated in the trial. Ms. Ruby's declaration also erroneously references C4591001's original exclusion criteria, *id.* at ¶15, without regard to subsequent protocol amendments to add study populations, interventions, and analyses not included in the original design, one of which permitted enrollment of HIV-infected trial participants. *See* FDA's Clinical Review at 23, referenced in Paragraph 19 above. Ms. Ruby is also incorrect in stating that FDA did not consider the pharmacokinetics of the vaccine (Ruby Decl. at ¶16). *See* FDA's CMC Review at 115, also referenced in Paragraph 19 above. In Paragraph 24 of her declaration, Ms. Ruby evidences a fundamental misunderstanding of the clinical trial process when she impliedly criticizes the protocol for C4591001 for permitting doses of the vaccine greater than 3 times the dose that was approved. In fact, one of the purposes of clinical trials to establish the appropriate dose of a medication and the very protocol cited by Ms. Ruby explains precisely how clinical data led to the dose that was ultimately approved. *See* Ruby Decl. Exhibit E at 40 (ECF No. 1-18 at 83). These examples are just illustrative of the many errors in Ms. Ruby's declaration.

26. An injunction against 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 here 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 consequence could be to seriously 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: October 21, 2021

Peter Marks

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

August 23, 2021

BioNTech Manufacturing GmbH
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

U.S. FOOD & DRUG ADMINISTRATION

October 20, 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] August 12, 2021,[7] and 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]

On October 20, 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 reissuing the September 22, 2021 letter of authorization in its entirety with revisions incorporated to clarify eligibility for the booster dose of COMIRNATY (COVID-19 Vaccine, mRNA) or Pfizer-BioNTech COVID-19 Vaccine and to authorize for emergency use 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

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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.

dose are the same as those authorized for a booster dose of the vaccine used for primary vaccination.

COMIRNATY (COVID-19 Vaccine, mRNA) is the same formulation as the Pfizer-BioNTech COVID-19 Vaccine and can be used interchangeably with the Pfizer-BioNTech COVID-19 Vaccine to provide doses for COVID-19 primary vaccination or a booster dose.[11]

For the December 11, 2020 authorization for individuals 16 years of age and older, FDA reviewed safety and efficacy 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. 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

[11] The licensed vaccine has the same formulation as the EUA-authorized vaccine and the products can be used interchangeably to provide doses for primary vaccination or a booster dose without presenting any safety or effectiveness concerns. The products are legally distinct with certain differences that do not impact safety or effectiveness.

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.

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 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 subsection III.BB, I am authorizing use of COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA when used to provide: (1) a two-dose regimen for individuals aged 12 through 15 years; (2) a third 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 homologous booster dose at least 6 months after completing a primary series to 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 with frequent institutional or occupational exposure to SARS-CoV-2; and (4) a heterologous booster dose to certain individuals who have completed primary vaccination with a different authorized COVID-19 vaccine 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[12] 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

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

C. There is no adequate, approved, and available alternative[13] Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19.[14]

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),[15] to emergency response stakeholders[16] as directed by the U.S. 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;
- The Pfizer-BioNTech COVID-19 Vaccine covered by this authorization will be administered by vaccination providers[17] and used only to prevent COVID-19 in individuals ages 12 and older with a two-dose primary regimen and to provide:

[13] 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 age 12 through 15; 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.

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

[15] "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.

[16] 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), 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.

[17] 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).

  - 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;
  - a single booster dose at least 6 months after completion of a primary series of the vaccine to individuals: 65 years of age or older; 18 through 64 years of age at high risk of severe COVID-19; and 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2; and
  - a single booster dose as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine, where 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.
- Pfizer-BioNTech COVID-19 Vaccine may be administered by a vaccination provider without an individual prescription for each vaccine recipient.

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 aged 12 through 15 years; (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 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 with frequent institutional or occupational exposure to SARS-CoV-2; 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, where 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.

Product Description[18]

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials; 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-BioNTech COVID-19 Vaccine does not contain a preservative.

Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (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 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic

[18] 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*.

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 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)
- 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)

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,[19] 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

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

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 in individuals 12 years of age and older as described in 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.[20]

[20] 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

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

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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).

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 (12 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 in individuals 12 years of age and older; 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 aged 12 through 15 years; (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 65 years of age or older, 18 through 64 years of age at high risk of severe COVID-19, and 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2; and (4) a heterologous booster dose to certain individuals 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.

Sincerely,

--/S/--

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

Enclosures

Marks Decl.
Exhibit C

U.S. FOOD & DRUG ADMINISTRATION

August 23, 2021

Pfizer Inc.
Attention: Ms. Elisa Harkins
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Harkins:

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 Federal Food, Drug, and Cosmetic 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 the biologics license application (BLA) submitted by BioNTech Manufacturing GmbH for COMIRNATY (COVID-19 Vaccine, mRNA) for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.

On August 23, 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 reissuing the August 12, 2021 letter of authorization in its entirety with revisions incorporated to clarify that the EUA will remain in place for the Pfizer-BioNTech COVID-19 vaccine for the previously-authorized indication and uses, and to authorize use of COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA for certain uses that are not included in the approved 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 to update 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).

Pfizer-BioNTech COVID-19 Vaccine contains a nucleoside-modified messenger RNA (modRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2 formulated in lipid particles. COMIRNATY (COVID-19 Vaccine, mRNA) is the same formulation as the Pfizer-BioNTech COVID-19 Vaccine and can be used interchangeably with the Pfizer-BioNTech COVID-19 Vaccine to provide the COVID-19 vaccination series.[8]

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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] The licensed vaccine has the same formulation as the EUA-authorized vaccine and the products can be used interchangeably to provide the vaccination series without presenting any safety or effectiveness concerns. The products are legally distinct with certain differences that do not impact safety or effectiveness.

For the December 11, 2020 authorization for individuals 16 years of age and older, FDA reviewed safety and efficacy 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 has 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 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 has enrolled approximately 46,000 participants, including 2,260 participants 12 through 15 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 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 dose of the Pfizer-BioNTech COVID-19 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, 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 mRNA 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 or 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.

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 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 subsection III.BB, I am authorizing use of COMIRNATY (COVID-19 Vaccine, mRNA) under this EUA when used to provide a two-dose regimen for individuals aged 12 through 15 years, or

to provide a third 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.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of Pfizer-BioNTech COVID-19 Vaccine 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[9] alternative to the emergency use of Pfizer-BioNTech COVID-19 Vaccine to prevent COVID-19.[10]

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),[11] to emergency response stakeholders[12] as directed by the U.S.

[9] 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 products that are approved to prevent COVID-19 in individuals age 12 through 15, or that are approved to provide an additional dose to the immunocompromised population described in this EUA.

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

[11] "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.

[12] 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), 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

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;
- The Pfizer-BioNTech COVID-19 Vaccine covered by this authorization will be administered by vaccination providers[13] and used only to prevent COVID-19 in individuals ages 12 and older; and
- Pfizer-BioNTech COVID-19 Vaccine may be administered by a vaccination provider without an individual prescription for each vaccine recipient.

This authorization also covers the use of the licensed COMIRNATY (COVID-19 Vaccine, mRNA) product when used to provide a two-dose regimen for individuals aged 12 through 15 years, or to provide a third 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.

Product Description

The Pfizer-BioNTech COVID-19 Vaccine is supplied as a frozen suspension in multiple dose vials; 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-BioNTech COVID-19 Vaccine does not contain a preservative.

Each 0.3 mL dose of the Pfizer-BioNTech COVID-19 Vaccine contains 30 mcg of a nucleoside-modified messenger RNA (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 0.2 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.

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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.

[13] 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).

The dosing regimen is two doses of 0.3 mL each, 3 weeks apart. A third dose may be administered at least 28 days following the second dose of the two dose regimen of this vaccine to 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.

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)

- 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).

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, 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 in individuals 12 years of age and older as described in 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.[14]

[14] 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

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

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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).

Case 4:21-cv-01211-AW-HTC Document 1-1 Filed 10/21/21 Page 56 of 61

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, 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 (12 years of age and older), 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 in individuals 12 years of age and older; 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 now 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. This authorization thus remains in place with respect to that product for the previously-authorized indication and uses (i.e., for use to prevent COVID-19 in individuals 12 years of age and older with a two-dose regimen, and to provide a third 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).

BB. This authorization also covers the use of the licensed COMIRNATY (COVID-19 Vaccine, mRNA) product when used to provide a two-dose regimen for individuals aged 12 through 15 years, or to provide a third 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. 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.

Sincerely,

Denise M. Hinton -S

Digitally signed by Denise M. Hinton -S
Date: 2021.08.23 11:05:39 -04'00'

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures

Marks Decl.

Exhibit D

Summary Basis for Regulatory Action

Date:	08/23/2021
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.

Director, Office of Vaccines Research and Review

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC	
• CMC Product (OVRR)	Xiao Wang, PhD, OVRR/DVP Anissa Cheung, MSc, OVRR/DVP
• Facilities Review (OCBQ/DMPQ)	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
• Facilities Inspection (OCBQ/DMPQ and OVRR/DVP)	Zhongren Wu, PhD, OCBQ/DMPQ Ekaterina Allen, PhD, OCBQ/DMPQ
• Lot Release, QC, Test Methods, Product Quality (OCBQ/DBSQC)	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)	Susan Wollersheim, MD, OVRR/DVRPA CAPT Ann T. Schwartz, MD, OVRR/DVRPA Lucia Lee, MD, OVRR/DVRPA
• Postmarketing Safety, Epidemiological Review (OBE/DE)	Deborah Thompson, MD, MSPH, OBE/DE
• Real World Evidence • Benefit-Risk Assessment	Yun Lu, PhD, OBE Hong Yang, PhD, OBE Osman Yogurtcu, PhD, OBE Patrick Funk, PhD, OBE
• BIMO	Haecin Chun, MT (ASCP) SSB, MS, OCBQ/DIS
Statistical	
• Clinical Data (OBE/DB)	Lei Huang, PhD, OBE/DB Ye Yang, PhD, OBE/DB
• Nonclinical Data	Xinyu Tang, PhD, OBE/DB
Nonclinical/Pharmacology/Toxicology	
• Toxicology (OVRR) • Developmental Toxicology (OVRR)	Nabil Al-Humadi, PhD, OVRR/DVRPA
Labeling	
• Promotional (OCBQ/APLB)	CAPT Oluchi Elekwachi, PharmD, MPH, OCBQ/APLB
• Carton and Container Labels • Labeling Review	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)), 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:

(b) (4)

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	Quantity after Dilution (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	Quantity after Dilution (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)	0.450 mL	Excipient

UNII: Unique Ingredient Identifier

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) (b) (4) RNA content and (b) (4) (b) (4) Assay, Lipid (ALC-0315, ALC-0159, DSPC, and Cholesterol) Content by (b) (4) , Container closure integrity test by (b) (4) (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) (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) (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) (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) (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

Case: 4:21-cv-01300-DDN Doc. #: 20-1 Filed: 11/18/21 Page: 77 of 161 PageID #: 564

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).

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%).

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 E

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

Table of Contents

Contains Nonbinding Recommendations

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 $\geq$ 30 per minute, heart rate $\geq$ 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.

Contains Nonbinding Recommendations

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.

Contains Nonbinding Recommendations

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.

Contains Nonbinding Recommendations

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 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,

Linda Wastila

Linda Wastila, BSPharm, MSPH, PhD
Representative
Coalition Advocating for Adequately Licensed Medicines (CAALM)

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Case 3:21-cv-01211-AW-HTC Document 1-3 Filed 10/21/21 Page 136 of 161

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Marks Decl.

Exhibit G

U.S. FOOD & DRUG ADMINISTRATION

August 23, 2021

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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

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[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

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.

Exhibit 2

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MISSOURI

STATE OF MISSOURI, et al. *Plaintiffs,* v. JOSEPH R. BIDEN, JR., et al. *Defendants.*	Civil Action No. 4:21-CV-1300

DECLARATION OF CODY BENJAMIN

IN SUPPORT OF DEFENDANTS' OPPOSITION TO PLAINITFFS' MOTION FOR PRELIMINARY INJUNCTION

I, **Cody Benjamin**, declare as follows to the best of my memory and knowledge:

1. I am currently employed as a Contracting Officer by the United States Department of Energy (DOE), Office of Science in the Ames Site Office for the Ames Laboratory. Since October 2021, I have served as Contracting Officer for DOE Management and Operating Contract No. DE-AC02-07CH11358 (the Contract) between DOE and Iowa State University of Science and Technology (ISU), the management and operating contractor for Ames Laboratory. Ames Laboratory is a government-owned, contractor-operated national laboratory of DOE, operated by and located on the campus of ISU in Ames, Iowa.

2. I have been employed by DOE since May 2021 where I began in the position of Contract Specialist. In October 2021, I received my warrant and assumed the position of Contracting Officer. In my capacity as a Contracting Officer, I am responsible for administration

of the Contract which includes issuing unilateral and bilateral contract modifications. My place of employment is the DOE Ames Site Office at the Ames Laboratory in Ames, Iowa.

3. I have reviewed the Declaration of Kraig Paulsen that is attached as Exhibit G to Plaintiffs' Memorandum in Support of a Preliminary Injunction in this case. (Ex. 9-7). Mr. Paulsen states that a large contract between DOE and the Ames Laboratory at ISU was unilaterally modified. ISU freely entered into the Contract with DOE that included provisions permitting DOE to unilaterally modify contractual requirements. DOE followed those provisions, as discussed below.

4. A bilateral modification (supplemental agreement) is a contract modification that is signed by the contractor and the contracting officer. Bilateral modifications are used to (1) make negotiated equitable adjustments resulting from the issuance of a change order; (2) definitize letter contracts; and (3) reflect other agreements of the parties modifying the terms of contracts. A unilateral modification is a contract modification that is signed only by the contracting officer. Unilateral modifications are used, for example, to (1) make administrative changes; (2) issue change orders; (3) make changes authorized by clauses other than a changes clause (e.g., a property clause, options clause, or suspension of work clause); and (4) to issue termination notices.

5. On October 6, 2021, DOE sent guidance to ISU about the incorporation of a clause, FAR 52.223-99, Ensuring Adequate COVID-19 Safety Protocols for Federal Contractors, into the Contract. ISU responded that it would not be open to a bilateral modification of the Contract to incorporate FAR 52.223-99. On October 8, 2021, DOE issued unilateral modification number 0294 to the Contract to incorporate FAR 52.223-99. DOE initially issued

the unilateral modification to incorporate FAR 52.223-99 because ISU would not accept a bilateral modification.

6. After a series of engagements with ISU, DOE agreed to remove FAR 52.223-99 via a bilateral modification and to incorporate the Contractor Requirements Document (CRD) associated with DOE Order 350.5 COVID Safety Protocols for Federal Contractors in the Contract via a separate, unilateral modification.

7. On October 14, 2021, DOE provided written notice to ISU informing them that the CRD associated with DOE Order 350.5 would be incorporated into the Contract. On November 15, 2021, DOE completed the unilateral modification to include CRD. Currently this modification is still in effect. On November 16, 2021, the bilateral modification to remove FAR 52.223-99 was sent to ISU for signature.

Pursuant to 28 U.S.C. Section 1746, I declare under the penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed in Ames, IA on the 18th day of November, 2021.

CODY BENJAMIN Digitally signed by CODY BENJAMIN Date: 2021.11.18 20:15:07 -06'00'

Cody Benjamin

Exhibit 3

UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF MISSOURI
EASTERN DIVISION

STATE OF MISSOURI, *et al.* Plaintiffs, v. JOSEPH R. BIDEN, JR., *et al.*, Defendants.	Case No. 4:21-cv-01300-DDN

DECLARATION OF ERICA HOFFMAN

I, ERICA HOFFMAN, hereby make this declaration under penalty of perjury pursuant to 28 U.S.C. § 1746:

1. I am over the age of 18 years and am otherwise competent to make this declaration.

2. I make this declaration on the basis of personal knowledge.

3. I have been employed with the U.S. General Services Administration ("GSA") since 2013. I am presently employed by GSA as a Contracting Officer in the Acquisition Management Division of Region 6 of GSA's Public Buildings Service.

4. I have reviewed the Declaration of Dru Buntin that is attached as Exhibit O to the Plaintiffs' Motion for Preliminary Injunction in this case (ECF No. 9-15).

5. I am familiar with the three contracts between GSA and the Missouri Department of Natural Resources referenced in paragraph 2 of Mr. Buntin's declaration

(the "GSA-Missouri DNR Contracts"). I am the designated Contracting Officer on all of the GSA-Missouri DNR Contracts. As such, I possess the authority to enter into, administer, and/or terminate these contracts and make related determinations and findings.

6. The contract numbers, award and end dates, and values of the GSA-Missouri DNR Contracts are as follows:

Contract Number	Award Date	Period of Performance End Date	Award Base and All Options Value
GS-06-P-17-GZ-P-0001	6/20/2017	12/31/2021	$58,000.00
47PG0218P0001	3/19/2018	12/31/2021	$59,019.52
47PG0218P0002	8/28/2018	12/31/2021	$124,125.00

7. The GSA-Missouri DNR Contracts are not Indefinite Delivery Indefinite Quantity ("IDIQ") type contracts or Federal Supply Schedule contracts. All of them are stand-alone agreements.

8. Each of the GSA-Missouri DNR Contracts is set to expire on December 31, 2021. None of them contains any option or provision to renew the agreement or extend the period of performance.

9. Given the total contract values listed above, each of the GSA-Missouri DNR Contracts is below what is known as the Simplified Acquisition Threshold ("SAT"). The SAT is subject to periodic adjustment for inflation. Currently, the SAT is $250,000. *See* 48 C.F.R. § 2.101.

10. Because the GSA-Missouri DNR Contracts are below the SAT, they are outside the scope of Executive Order 14042, as noted in section 5(b)(iii) of that order. As a result, while the inclusion in these agreements of the contract clause requiring all covered contractors to comply with all guidance for contractor or subcontractor workplace locations published by the Safer Federal Workforce Task Force ("SFWTF") is "strongly encouraged" (as noted on page 5 of the latest SFWTF Guidance, issued November 10, 2021), such inclusion is not mandatory.

11. I declare under penalty of perjury that the foregoing is true and correct.

Executed on: November 17, 2021

ERICA HOFFMAN

Digitally signed by ERICA HOFFMAN
DN: C=US, O=U.S. Government, OU=General Services Administration, CN=ERICA HOFFMAN +
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Foxit PDF Editor Version: 11.0.1

Erica Hoffman
Contracting Officer
Region 6 Acquisition Management Division
Public Buildings Service