March 24, 2022

Carol Taccetta, MD, FCAP
(b) (6) [redacted]

Sent via email to: (b) (6) [redacted]

Re: Docket No. FDA-2022-P-0086

Dear Dr. Taccetta,

This letter responds to the citizen petition dated January 19, 2022 that you (Petitioner) submitted to the Food and Drug Administration (FDA, the Agency, we) relating to Emergency Use Authorization, licensure, and clinical trials of Coronavirus Disease 2019 (COVID-19) vaccines (the Petition).

In the Petition, Petitioner requests that FDA:[1]

1. "[r]evoke all Covid-19 vaccine Biologics License Application (BLA) approvals and emergency use authorizations (EUA) for all pediatric subgroups, ages 0 to 17";
2. "[a]dd Pregnancy as a Contraindication for all Covid-19 vaccine BLAs and EUAs";
3. "[i]mmediately suspend all ongoing clinical trials for all pediatric and pregnant subpopulations"; and,
4. "[a]dd pregnancy and pediatric exclusion criteria for all ongoing or planned Covid-19 vaccine clinical trials."

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

Here is an outline of our response:

[1] Petition at 1.

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I. BACKGROUND

There is currently a pandemic of respiratory disease, COVID-19, caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (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.[2] On February 4, 2020, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (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 United States (U.S.) citizens living abroad, and that involves the virus that causes COVID-19.[3] 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.[4] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[5]

Commercial vaccine manufacturers and other entities have developed COVID-19 vaccine candidates, and clinical studies of these vaccines are underway and/or have been publicly reported. Between December 11, 2020 and February 27, 2021, FDA issued EUAs for three vaccines to prevent COVID-19 ("the Authorized COVID-19 Vaccines"), including vaccines sponsored by Pfizer Inc. (Pfizer),[6] ModernaTX, Inc. (Moderna), and Janssen Biotech, Inc. (Janssen). The EUAs have been amended since initial issuance. For example, on May 10, 2021, FDA amended the EUA for the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 to include individuals 12 through 15 years of age. On October 29, 2021, FDA

[2] Secretary of HHS Alex M. Azar, Determination that a Public Health Emergency Exists (Originally issued on Jan. 31, 2020, and subsequently renewed), https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.
[3] 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.
[4] 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.
[5] 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/.
[6] Hereinafter "Pfizer-BioNTech COVID-19 Vaccine".

amended the EUA for the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 to include individuals 5 through 11 years of age.

On August 23, 2021, the Agency approved Comirnaty (COVID-19 Vaccine, mRNA) ("Comirnaty") and the approval was granted to BioNTech Manufacturing GmbH.[7] Comirnaty is approved for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. On January 31, 2022, the Agency approved Spikevax (COVID-19 Vaccine, mRNA) ("Spikevax") and the approval was granted to ModernaTX, Inc. Spikevax is approved for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

II. VACCINES THAT ARE FDA-LICENSED OR RECEIVE AN EMERGENCY USE AUTHORIZATION MEET RELEVANT STATUTORY REQUIREMENTS

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[8]) 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.[9] The IND describes the proposed clinical study in detail and, among other things, helps protect the safety and rights of human subjects.[10] 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 investigational drug) permits FDA to assess whether they are qualified to fulfill their clinical trial duties. The IND includes commitments to obtain informed consent from the research subjects, to obtain review of

[7] BioNTech Manufacturing GmbH is the biologics license holder for this vaccine, which is manufactured by Pfizer for BioNTech Manufacturing GmbH (hereinafter "BioNTech").

[8] 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.

[9] See 21 CFR 312.20(a).

[10] 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. When final, this guidance will represent FDA's current thinking on this topic.

the study by an institutional review board (IRB),[11] 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.[12]

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

Additionally, FDA regulations require that an IRB must review clinical investigations involving children as subjects covered by 21 CFR Part 50, subpart D and only approve those clinical investigations involving children as subjects that satisfy the criteria in 21 CFR Part 50, subpart D, Additional Safeguards for Children in Clinical Investigations. As explained in the preamble to the final rule, "[t]hese safeguards are intended to ensure that the rights and welfare of children who participate in clinical investigations are adequately protected."[13]

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

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[11] 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.

[12] 21 CFR 312.22(a).

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

505(i)(3) of the FD&C Act), 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.[14]

B. Licensed Vaccines Are Safe, Pure, and Potent

FDA has a stringent regulatory process for licensing vaccines.[15,16] 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."[17] 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 BLA for 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 application 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.[18]

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.[19] 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."[20] 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.

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[14] 21 CFR 312.42(a).
[15] 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.
[16] Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[17] Section 351(a)(2)(C)(i)(I) of the PHS Act.
[18] 21 CFR 601.2(a).
[19] FDA, Vaccines, last updated January 2021, https://www.fda.gov/vaccines-blood-biologics/vaccines.
[20] 21 CFR 601.2(d).

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

Congress established the EUA pathway to ensure that, during public health emergencies, potentially lifesaving medical products could be made available before being approved. The EUA process allows the Secretary of HHS, in appropriate circumstances, to declare that EUAs are justified for products to respond to certain types of threats. When such a declaration is made, FDA may issue an EUA, which is different from the regulatory process for vaccine licensure.

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

On February 4, 2020, pursuant to section 564(b)(1)(C) of the FD&C Act, 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.[21] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564(b)(1) of the FD&C Act.[22]

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

- The agent referred to in the COVID-19 EUA Declaration by the Secretary (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

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

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

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

[21] 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.
[22] 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.

Although EUAs are governed under a different statutory framework than BLAs, FDA has made clear that issuance of an EUA for a COVID-19 vaccine would require that the vaccine demonstrated clear and compelling safety and efficacy in a large, well-designed Phase 3 clinical trial. In the guidance document Emergency Use Authorization for Vaccines to Prevent COVID-19, FDA has provided recommendations that describe key information that would support issuance of an EUA for a vaccine to prevent COVID-19.[23] In the guidance, FDA explained that, in the case of such investigational vaccines, any assessment regarding an EUA will be made on a case-by-case basis considering the target population, the characteristics of the product, the preclinical and human clinical study data on the product, and the totality of the available scientific evidence relevant to the product.[24] FDA has also stated, in this guidance, that for a COVID-19 vaccine for which there is adequate manufacturing information to ensure its quality and consistency, issuance of an EUA would require a determination by FDA that the vaccine's benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial that demonstrates the vaccine's safety and efficacy in a clear and compelling manner.[25]

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

In a Phase 3 study of a COVID-19 vaccine, the efficacy of the investigational vaccine to prevent disease will be assessed by comparing the number of cases of disease in each study group. For Phase 3 placebo controlled efficacy trials, FDA has recommended to manufacturers in guidance that the vaccine should be at least 50% more effective than the comparator, and that the outcome be reliable enough so that it is not likely to have happened by chance.[26] During the entire study, subjects will be monitored for safety events. If the evidence from the clinical trial meets the pre-specified criteria for success for efficacy and the safety profile is acceptable, the results from the trial can potentially be submitted to FDA in support of an EUA request.

Following clinical trials, manufacturers analyze data prior to submitting to FDA a BLA to request approval from FDA to market the vaccine. A BLA for a new vaccine includes information and data regarding the safety, effectiveness, chemistry, manufacturing and controls, and other details regarding the product. During the current public health emergency, manufacturers may, with the requisite data and taking into consideration input from FDA, choose to submit a request for an EUA.

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

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[23] Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry, May 2021, https://www.fda.gov/media/142749/download.
[24] Id. at 4.
[25] Id.
[26] Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry, June 2020, https://www.fda.gov/media/139638/download.

III. DISCUSSION

Petitioner makes several requests regarding COVID-19 vaccines in the Petition, including requests relating to EUA, licensure, and clinical trials of COVID-19 vaccines. Below, we address each of Petitioner's requests and the information provided by Petitioner in support of these requests. We note that Petitioner states that the requests are "per 45 CFR 46"; however, FDA does not administer or enforce the regulations in 45 CFR Part 46, and those regulations do not control the requested actions. Therefore, the analysis in this response focuses instead on the statutory and regulatory provisions relevant to the requested actions.

A. Request to Revoke EUAs and BLA Approvals for Pediatric Populations

Petitioner requests that FDA "[r]evoke all Covid-19 vaccine Biologics License Application (BLA) approvals and emergency use authorizations (EUA) for all pediatric subgroups, ages 0 to 17."[27] Petitioner asserts that the "protective criteria set forth in 45 CFR 46 have never been met for pregnant women, fetuses and children, resulting in 'serious concerns about subject safety.'"[28] Petitioner further states that "if clinical trials in pregnant and pediatric patients were previously executed without proper legal protections, any current EUA or BLA could not be supported and would need to be revoked for these same subgroups."[29]

1. Request to Revoke EUAs for Pediatric Subgroups

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

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

At the outset, we note that Congress has provided FDA with discretion under section 564 of the FD&C Act and nothing in the statute *requires* FDA to *revoke* existing EUAs in any circumstance. Rather, section 564(g)(2) of the FD&C Act says that, in certain circumstances, "*may* revise or revoke" an EUA.[30] The verb "may" is ordinarily permissive, particularly when the statute elsewhere uses the term "shall" to confer a mandatory duty.[31] Further underscoring

[27] Petition at 1.
[28] Petition at 3.
[29] Petition at 2.
[30] Section 564(g)(2) of the FD&C Act (emphasis added).
[31] See *Old Line Life Ins. Co. of Am. v. Garcia*, 411 F.3d 605, 614-15 (6th Cir. 2005); *Goodman v. City Prods. Corp, Ben Franklin Div.*, 425 F.2d 702, 703 (6th Cir. 1970); *Anderson v. Yungkau*, 329 U.S. 482, 485 (1947) ("[W]hen the same Rule uses both 'may' and 'shall,' the normal inference is that each is used in its usual sense—the one act being permissive, the other mandatory."); see also A. Scalia & B.A. Garner, *Reading Law: The Interpretation of Legal*

FDA's discretion, the EUA statute explicitly provides that all decisions regarding EUAs are "committed to agency discretion."[32]

A permissive reading of "may" also accords with the statutory purpose of giving FDA flexibility to "permit rapid distribution of promising new drugs and antidotes in the most urgent circumstances,"[33] because it allows the Agency to permit continued distribution of EUA products and thereby removes the need for manufacturers to limit supply or delay seeking approval to exhaust supplies of authorized product.

FDA's guidance entitled Emergency Use Authorization of Medical Products and Related Authorities ("EUA Guidance"),[34] notes that once an EUA is issued for a product, in general, that EUA will remain in effect for the duration of the EUA declaration under which it was issued, "unless the EUA is revoked because the criteria for issuance . . . are no longer met or revocation is appropriate to protect public health or safety (section 564(f),(g) [of the FD&C Act])."[35]

Currently, the Pfizer-BioNTech COVID-19 Vaccine is the only authorized vaccine indicated for the prevention of COVID-19 in any pediatric populations. The EUA for the Pfizer-BioNTech COVID-19 Vaccine provides for administration of the vaccine as a two-dose primary series in individuals 5 years of age and older, as a third primary series dose for individuals 5 years of age and older who have been determined to have certain kinds of immunocompromise, as a single booster dose in individuals 12 years of age and older after completion of a primary series of Pfizer-BioNTech COVID-19 Vaccine, and as a single heterologous booster dose following completion of primary vaccination with another authorized COVID-19 Vaccine in individuals 18 years of age and older.

In this section, we assess whether any of the statutory conditions under which FDA may revoke an EUA are met with respect to the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA, namely: (1) whether the circumstances justifying issuance under section 564(b)(1) of the FD&C Act no longer exist, (2) whether the criteria for issuance under section 564(c) of the FD&C Act are no longer met, and (3) whether other circumstances make a revision or revocation appropriate to protect the public health or safety.

Texts 112 (2012) ("The traditional, commonly repeated rule is that *shall* is mandatory and *may* is permissive. . ."). There is nothing to indicate that section 564(g)(2) of the FD&C Act departs from this ordinary meaning of "may." To the contrary, section 564 of the FD&C Act consistently uses "may" as permissive and "shall" as mandatory. Compare, e.g., section 564(a) of the FD&C Act (providing that the Secretary "may" issue an EUA) and id. section 564(b)(1) of the FD&C Act (providing that the Secretary "may" declare a public emergency), with, e.g., id. section 564(b)(3) of the FD&C Act (providing that the Secretary "shall" provide notice in advance of terminating a declaration) *and id.* section 564(h)(1) of the FD&C Act (providing that the Secretary "shall" publish certain EUA actions in the Federal Register).

[32] See section 564(i) of the FD&C Act. *See also Association of American Physicians & Surgeons v. FDA*, 2020 WL 5745974, at *3 (6th Cir. Sept. 24, 2020) (citing to section 564(i) of the FD&C Act for the proposition that "emergency-use authorizations are exempt from review under the [Administrative Procedure Act].").

[33] *See* 2004 U.S.C.C.A.N. S17, S18 (Statement of President Bush Upon Signing P.L. 108-276, PROJECT BIOSHIELD ACT OF 2004).

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

[35] Id. at 28.

i. Circumstances Justifying the Emergency Use Continue to Exist

As explained above in section I, on February 4, 2020, pursuant to section 564(b)(1)(C) 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.[36] On the basis of such determination, on March 27, 2020, the Secretary then made the COVID-19 EUA Declaration, pursuant to section 564(b)(1) of the FD&C Act.[37]

The circumstances described under section 564(b)(1) of the FD&C Act continue to exist (i.e., the COVID-19 EUA Declaration remains in effect). FDA therefore is not revoking the EUA for the authorized COVID-19 vaccine with pediatric indications under the authority in section 564(g)(2)(A) of the FD&C Act.

ii. The Criteria for Issuance of the EUA Continue to be Met

This section describes why the criteria under section 564(c) of the FD&C Act continue to be met with respect to the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine and why, therefore, FDA is not revoking this EUA under the authority in section 564(g)(2)(B) of the FD&C Act at this time.

Criterion 1: The agent referred to in the COVID-19 EUA Declaration by the Secretary (SARS-CoV-2) can cause a serious or life-threatening disease or condition (section 564(c)(1) of the FD&C Act).

FDA has concluded that SARS-CoV-2, which is the subject of the EUA declaration, can cause a serious or life-threatening disease or condition. FDA is not aware of science indicating that there is any change in the ability of the SARS-CoV-2 virus to cause a serious or life-threatening disease or condition, namely COVID-19, nor has Petitioner provided any information about such a change.

The SARS-CoV-2 pandemic continues to present an extraordinary challenge to global health and, as of March 14, 2022, has caused more than 450 million cases of COVID-19 and claimed the lives of more than 6 million people worldwide.[38] In the U.S., as of March 9, 2022 more than 79 million cases and over 960,000 deaths have been reported to the CDC.[39] On January 31, 2020, the U.S. Secretary of HHS declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS, and the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Additional background information on the SARS-

[36] 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.
[37] 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.
[38] Johns Hopkins University School of Medicine, Coronavirus Resource Center, https://coronavirus.jhu.edu/map.html (accessed March 14, 2022).
[39] CDC, COVID Data Tracker, https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html (accessed March 14, 2022).

CoV-2 virus and COVID-19 pandemic may be found in FDA decision memoranda for the Pfizer-BioNTech COVID-19 Vaccine.[40]

As of March 14, 2022, approximately 5 million and 4.48 million COVID-19 cases in individuals 12 to 17 years of age and individuals 5 through 11 years of age, respectively have been reported to the CDC.[41] Some of these cases have resulted in hospitalization and death. The cumulative rate of COVID-19 associated hospitalization was 52.9 per 100,000 for the 5 – 11 population and 115.3 per 100,000 for the 12 – 17 population as of March 5, 2022 based on COVID-NET data reported to the CDC.[42] As of March 14, 2022, 1,139 deaths associated with COVID-19 have been reported among individuals ages 5 through 17.[43] It is difficult to estimate the incidence of COVID-19 among pediatric populations because they are frequently asymptomatic and infrequently tested. Pediatric populations appear less susceptible to SARS-CoV-2 infection and generally have a milder COVID-19 disease course as compared with adults. However, as with adults, pediatric populations with underlying conditions such as asthma, chronic lung disease, and cancer are at higher risk than their heathier counterparts for COVID-19-related hospitalization and death. Of the children who have developed severe illness from COVID-19, most have had underlying medical conditions. Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious COVID-19-associated condition that can present with persistent fever, laboratory markers of inflammation and heart damage, and, in severe cases, hypotension and shock. As of March 1, 2022, the CDC received reports of 7,459 cases and 63 deaths that met the definition for MIS-C.[44]

Both FDA and CDC have convened advisory committee meetings to discuss the use of COVID-19 vaccines in pediatric populations. Overall, these advisory committees agreed that there is a serious risk of severe COVID-19 in pediatric populations. The June 23, 2021 Advisory Committee on Immunization Practices (ACIP) meeting discussed the benefits and risks of the use of COVID-19 mRNA vaccines in adolescents and young adults.[45] This discussion raised the point that adolescents and young adults have the highest COVID-19 incidence rates, and that these populations are an increasing proportion of COVID-19 cases reported. During the November 2, 2021 ACIP meeting the committee discussed the benefits and risks of the use of the

[40] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda to Decision Memoranda, dated December 11, 2020; May 10, 2021; August 12, 2021; September 22, 2021; October 20, 2021; October 29, 2021; November 18, 2021; November 19, 2021; December 8, 2021; December 30, 2021; and January 6, 2022 (referred to collectively in this response as "FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda"). FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda are incorporated by reference in this response.

[41] CDC, Demographic Trends of COVID-19 cases and deaths in the US reported to CDC, https://covid.cdc.gov/covid-data-tracker/#demographics (accessed March 14, 2022).

[42] CDC, COVID-NET Laboratory-confirmed COVID-19 hospitalizations, https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network (accessed March 14, 2022). The current network covers nearly 100 counties.

[43] CDC, Demographic Trends of COVID-19 cases and deaths in the US reported to CDC, https://covid.cdc.gov/covid-data-tracker/#demographics (accessed March 14, 2022).

[44] CDC, Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States, https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance (accessed March 14, 2022).

[45] CDC, Megan Wallace and Sara Oliver, CDC ACIP Meeting Presentation, COVID-19 mRNA vaccines in adolescents and young adults: Benefit-Risk Discussion, (June 23, 2021), https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/05-COVID-Wallace-508.pdf; CDC, ACIP Meeting Slides, (June 23, 2021), https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html.

Pfizer-BioNTech COVID-19 Vaccine in children 5 through 11 years of age.[46] ACIP concluded that COVID-19 in children is a major public health problem.[47] At that time approximately 1.9 million COVID-19 cases and 8,300 hospitalizations among U.S. children aged 5–11 years had been reported to CDC as of October 10, 2021.[48]

Therefore, the criterion under section 564(c)(1) of the FD&C Act continues to be met with respect to the authorized COVID-19 vaccine with pediatric indications.

Criterion 2: Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing such serious or life-threatening disease or condition that can be caused by SARS-CoV-2 (section 564(c)(2)(A) of the FD&C Act).

FDA has determined that based on the totality of scientific evidence available, including data from adequate and well-controlled trials, it is reasonable to believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2 in individuals 5 years of age and older. The basis for this determination is explained in detail in FDA's decision memoranda regarding the Pfizer-BioNTech COVID-19 Vaccine EUA.[49] FDA is not aware of any data that change this conclusion, nor has Petitioner provided any such data in the Petition. Therefore, the criterion under section 564(c)(2)(A) of the FD&C Act continues to be met with respect to the authorized COVID-19 vaccine with pediatric indications.

Criterion 3: The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product (section 564(c)(2)(B) of the FD&C Act).

FDA authorized the Pfizer-BioNTech COVID-19 Vaccine after reaching a determination that, among other things, the known and potential benefits of the vaccine, when used to prevent COVID-19, outweigh its known and potential risks. The basis for this determination is explained in detail in FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda.

Petitioner refers to risks of anaphylaxis, myocarditis, and pericarditis that were considered by FDA when authorizing the Pfizer-BioNTech COVID-19 Vaccine for emergency use in certain pediatric populations.[50] Petitioner presents no new data relating to the known and potential risks of the Pfizer-BioNTech COVID-19 Vaccine. In addition, Petitioner asserts that COVID-19 "rarely manifests as severe disease in children, the infection fatality rate (IFR) 'near zero.'"[51]

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[46] See CDC, ACIP Presentation Slides: November 2-3, 2021 Meeting, https://www.cdc.gov/vaccines/acip/meetings/slides-2021-11-2-3.html.
[47] CDC, The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Children Aged 5-11 Years – United States, November 2021, https://www.cdc.gov/mmwr/volumes/70/wr/mm7045e1.htm.
[48] Id.
[49] FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda.
[50] Id.
[51] Petition at 4.

However, Petitioner presents no information that alters FDA's assessment of the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, or whether such known and potential benefits outweigh the known and potential risks. Known and potential benefits, in pediatric populations in which the vaccine is authorized for use, include reduction in the risk of symptomatic COVID-19 and associated serious complications.[52] As explained in more detail above, pediatric populations generally have a milder COVID-19 disease course as compared with adults; however, thousands of COVID-19 associated hospitalizations and more than 1,000 COVID-19 associated deaths have occurred in individuals ages 5 through 17. Additionally, MIS-C can occur in pediatric populations following COVID-19.

Petitioner has not provided any data, nor is FDA aware of any data, that changes FDA's conclusion that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, when used to prevent COVID-19, outweigh its known and potential risks, including in certain pediatric populations. Therefore, the criterion under section 564(c)(2)(B) of the FD&C Act continues to be met with respect to the authorized COVID-19 vaccine with pediatric indications.

Criterion 4: There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition (section 564(c)(3) of the FD&C Act).

The only FDA-approved drugs or biological products indicated to prevent COVID-19 in any population are Comirnaty and Spikevax. Spikevax is approved for the prevention of COVID-19 disease in individuals 18 years of age and older, and Comirnaty is approved for the prevention of COVID-19 disease in individuals 16 years of age and older.

Although there are two approved COVID-19 vaccines, that does not mean that there is now an "adequate, approved, and available" alternative such that continuation of the EUAs is no longer justified. For example, the Pfizer-BioNTech COVID-19 Vaccine is authorized for the prevention of COVID-19 in individuals 5 through 15 years of age; for use as a single booster dose in individuals 12 through 17 years of age; and for use as a third primary series dose to certain immunocompromised individuals 5 through 17 years of age. There are no FDA-approved, available alternatives for these populations.

Moreover, one consideration in FDA's assessment of whether there is an adequate, approved, and available alternative relates to availability, or demand and supply. There is still need and demand for COVID-19 vaccines and having sufficient supply is crucial for ensuring that vaccines are available to protect individuals against COVID-19.

Therefore, there is no adequate, approved, and available alternative to the Pfizer-BioNTech COVID-19 Vaccine for preventing COVID-19. The criterion under section 564(c)(3) of the FD&C Act continues to be met with respect to the authorized COVID-19 vaccine with pediatric indications.

[52] FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda.

iii. No Other Circumstances Make a Revision or Revocation Appropriate to Protect the Public Health or Safety

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

> significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.[53]

As of the date of this writing, FDA has not identified any such circumstances that would make revocation of the EUA of the Pfizer-BioNTech COVID-19 Vaccine in the pediatric population appropriate to protect the public health or safety, nor has Petitioner provided any such data. FDA determined the EUA standard is met for the vaccine because data submitted by the sponsor demonstrated in a clear and compelling manner that the known and potential benefits of the product, when used to prevent COVID-19, outweigh the known and potential risks of the product, and that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating COVID-19.

For the reasons explained above, FDA finds no basis in the information submitted in the Petition, or in any data regarding the Pfizer-BioNTech COVID-19 Vaccine, to support a revocation of the EUA of the Pfizer-BioNTech COVID-19 Vaccine in the pediatric population. FDA therefore sees no justifiable basis upon which to take any action based on Petitioner's request with respect to the EUA of the Pfizer-BioNTech COVID-19 Vaccine in the pediatric population. Accordingly, we deny Petitioner's request that FDA "[r]evoke all Covid-19…emergency use authorizations (EUA) for all pediatric subgroups, ages 0 to 17."[54]

[53] EUA Guidance at 29.
[54] Petition at 1.

2. Request to Revoke BLA Approvals for Pediatric Subgroups

As noted, the only licensed vaccines indicated to prevent COVID-19 in any population are Comirnaty and Spikevax ("the Approved COVID-19 Vaccines"). FDA licensed these products after determining that they satisfy the standards for approval in section 351(a) of the PHS Act, including based on a demonstration that the products are safe, pure, and potent.[55] Comirnaty is the only COVID-19 vaccine approved for use in any pediatric population. Specifically, Comirnaty is approved for the prevention of COVID-19 disease in individuals 16 years of age and older. Thus, in this section, we assess whether there are any circumstances that would justify license revocation with respect to Comirnaty.

The conditions for license revocation are set forth in 21 CFR 601.5. Pursuant to 21 CFR 601.5(a), a biologics license shall be revoked upon application of the manufacturer giving notice of intention to discontinue the manufacture of all products manufactured under such license or to discontinue the manufacture of a particular product for which a license is held and waiving an opportunity for a hearing on the matter.

Additionally, under 21 CFR 601.5(b), FDA must notify the licensed manufacturer of the intention to revoke the biologics license if it finds any of the following:

> (i) Authorized Food and Drug Administration employees after reasonable efforts have been unable to gain access to an establishment or a location for the purpose of carrying out the inspection required under 21 CFR 600.21,
>
> (ii) Manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection or evaluation cannot be made,
>
> (iii) The manufacturer has failed to report a change as required by 21 CFR 601.12,
>
> (iv) The establishment or any location thereof, or the product for which the license has been issued, fails to conform to the applicable standards established in the license and in this chapter designed to ensure the continued safety, purity, and potency of the manufactured product,
>
> (v) The establishment or the manufacturing methods have been so changed as to require a new showing that the establishment or product meets the requirements established in this chapter in order to protect the public health, or
>
> (vi) The licensed product is not safe and effective for all of its intended uses or is misbranded with respect to any such use.

FDA has not identified any such circumstances described in 21 CFR 601.5(a) or (b) that would support revocation of the biologics license for Comirnaty, and Petitioner has provided no

[55] FDA's Summary Basis for Regulatory Action (SBRA) for the Comirnaty BLA, and FDA's SBRA for the Spikevax BLA, set forth the basis for these licensure decisions. These memoranda are posted on www.fda.gov. We incorporate by reference the SBRA for the Comirnaty BLA and the SBRA for the Spikevax BLA.

evidence that such circumstances exist. Therefore, at this time, FDA has no basis for such revocation. Accordingly, we deny Petitioner's request that FDA "[r]evoke all Covid-19 vaccine Biologics License Application (BLA) approvals…for all pediatric subgroups, ages 0 to 17."[56]

B. Request to Add a Pregnancy Contraindication

Petitioner requests that FDA "[a]dd Pregnancy as a Contraindication for all Covid-19 vaccine BLAs and EUAs."[57]

BLAs

FDA regulations govern the content and format of prescription drug labeling for approved drugs and biological products.[58] The regulations are intended to organize labeling information to more effectively communicate to health care professionals the "information necessary for the safe and effective use of prescription drugs."[59]

The Contraindications section of the labeling must describe any situations in which the drug should not be used because the risk of use "clearly outweighs any possible therapeutic benefit."[60] This section should include observed and anticipated risks, but not theoretical risks.[61] This could include, for example, a situation where animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrate that the drug has teratogenic effects) and those risks outweigh any potential benefit of the drug to any patient.[62]

The Approved COVID-19 Vaccines are indicated for use in an age range that includes women of childbearing age and are not contraindicated for use in pregnant women.[63] The Approved COVID-19 Vaccines do not contain a contraindication in the labeling for use during pregnancy because FDA is not aware of any evidence that suggests that the risk of use of the Approved COVID-19 Vaccines in pregnant women would clearly outweigh any possible therapeutic benefit,[64] nor has Petitioner presented any such evidence in the Petition.

EUAs

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[56] Petition at 1.
[57] Petition at 1.
[58] See, e.g., 21 CFR 201.56 and 21 CFR 201.57; see also 21 CFR 201.100(c).
[59] Preamble to final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922 at 3928, January 24, 2006) (Physician Labeling Rule), https://www.federalregister.gov/documents/2006/01/24/06-545/requirements-on-content-and-format-of-labeling-for-human-prescription-drug-and-biological-products. For the content and format requirements for the labeling of older prescription drug products that are not subject to the labeling requirements in 21 CFR 201.57, see 21 CFR 201.80. The specific labeling requirements for older drug products differ in certain respects, and generally are not referenced in this response.
[60] 21 CFR 201.57(c)(5).
[61] See 21 CFR 201.57(c)(5); see also FDA guidance for industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format; Guidance for Industry, October 2011 (Warnings Guidance), at 8, https://www.fda.gov/media/71866/download.
[62] See Warnings Guidance at 9.
[63] See Comirnaty Package Insert, at 2, https://www.fda.gov/media/151707/download; See Spikevax Package Insert, at 2, https://www.fda.gov/media/155675/download.
[64] See FDA's SBRA for the Comirnaty BLA and FDA's SBRA for the Spikevax BLA.

For the emergency use of an unapproved product, section 564(e)(1)(A)(i) of the FD&C Act requires that FDA must—to the extent practicable given the applicable circumstances of the emergency, and as FDA finds necessary and appropriate to protect the public health—establish appropriate conditions designed to ensure that health care professionals administering the authorized product are informed:

- That FDA has authorized the emergency use of the product (including the product name and an explanation of its intended use);
- of the significant known and potential benefits and risks of the emergency use of the product, and the extent to which such benefits and risks are unknown; and
- of available alternatives and their benefits and risks.

Therefore, as explained in the EUA Guidance, FDA recommends that "a request for an EUA include a 'Fact Sheet' for health care professionals or authorized dispensers that includes essential information about the product. In addition to the required information, Fact Sheets should include . . . any contraindications or warnings."[65] The EUA guidance also recommends that, for unapproved drugs that do not have "FDA-approved labeling for any indication . . . in addition to the brief summary information found in a Fact Sheet, the sponsor also develop more detailed information similar to what health care professionals are accustomed to finding in FDA-approved package inserts."[66]

The Authorized COVID-19 Vaccines are authorized for use in an age range that includes women of childbearing age.[67] The sponsors for all the Authorized COVID-19 Vaccines submitted prescribing information in the EUA requests, and FDA reviewed and authorized this labeling. The Fact Sheets for Healthcare Providers Administering Vaccine for all of the Authorized COVID-19 Vaccines contain Contraindications and Warnings and Precautions sections because FDA determined that sufficient data existed for inclusion of such information in the authorized labeling for these vaccines.[68] FDA did not, however, require inclusion of a contraindication for pregnancy in the authorized labeling because FDA is not aware of any evidence that suggests that the risk of use of the Authorized COVID-19 Vaccines in pregnant women would clearly

[65] EUA Guidance at 22.
[66] EUA Guidance at 23.
[67] See, e.g., Pfizer-BioNTech COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), at 1-2, https://www.fda.gov/media/146304/download and https://www.fda.gov/media/153715/download; Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), at 1-2, https://www.fda.gov/media/146304/download; Moderna COVID-19 Fact Sheet For Healthcare Providers Administering Vaccine (Vaccination Providers), at 1-2, https://www.fda.gov/media/144637/download.
[68] Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Sections 5.2 and 5.3 Warnings and Precautions Regarding Thrombosis with Thrombocytopenia and GBS, https://www.fda.gov/media/146304/download; Pfizer-BioNTech COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, https://www.fda.gov/media/144413/download; Moderna COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, https://www.fda.gov/media/144637/download.

outweigh any possible therapeutic benefit, nor has the Petitioner presented any such evidence in the Petition.[69]

We therefore deny the request in the Petition for FDA to "[a]dd Pregnancy as a Contraindication for all Covid-19 vaccine BLAs and EUAs."[70]

C. Requests to Suspend Clinical Trials for All Pediatric and Pregnant Subpopulations and to Add Exclusion Criteria for Pediatric and Pregnant Subpopulations

Petitioner requests that FDA "[i]mmediately suspend all ongoing clinical trials for all pediatric and pregnant subpopulations."[71] We interpret this request as being specific to clinical trials for COVID-19 vaccines, which are the focus of the Petition. Petitioner also requests that FDA "[a]dd pregnancy and pediatric exclusion criteria for all ongoing or planned Covid-19 vaccine clinical trials."[72] In support of the requests, Petitioner makes assertions regarding the risk of severe disease in pediatric populations, and regarding anaphylaxis, myocarditis, and pericarditis.[73] The Petition also asserts with respect to "Research involving pregnant women or fetuses" that "[p]er current Fact Sheets/Package Insert, for each vaccine, only a single rat or rabbit developmental toxicity study has been performed."[74]

Regarding the request for certain exclusion criteria, the study protocol, including any exclusion criteria, would be submitted to FDA and reviewed by FDA as part of its review of the IND. To the extent Petitioner is requesting that FDA prohibit sponsors of COVID-19 vaccine clinical investigations from conducting such investigations without the exclusion criteria specified in the Petition, the mechanism by which FDA would do so is by placing the investigations on clinical hold. Accordingly, we interpret both the request to "[i]mmediately suspend all ongoing clinical trials for all pediatric and pregnant subpopulations" and the request to "[a]dd pregnancy and pediatric exclusion criteria for all ongoing or planned Covid-19 vaccine clinical trials" to be requests for FDA to place on clinical hold all COVID-19 vaccine studies that include pregnant and pediatric subjects, including those that do not specifically exclude pregnant or pediatric individuals. This section addresses both of these requests and explains why FDA is not at this time granting either request.

As explained above in section II.A, with certain exceptions, clinical investigations in which a drug is administered to human subjects must be conducted under an IND submitted to FDA by the sponsor. FDA's review of an IND includes a review of the study protocol(s) which describes, among other things, the design of the clinical study, including the identified endpoints

[69] FDA's decision memoranda for the Authorized COVID-19 Vaccines discuss FDA's analysis of all available data regarding the use of the Authorized COVID-19 Vaccines in pregnancy. See, e.g., Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda.
[70] Petition at 1.
[71] Petition at 1.
[72] Petition at 1.
[73] Petition at 3-5.
[74] Petition at 3.

and methods for assessing the safety and effectiveness of the investigational product. Petitioner requests that FDA adopt a universal approach toward all clinical trials of COVID-19 vaccines. Under FDA's regulations, however, the Agency examines each IND individually and considers the IND in the context of the standards in the regulation.

The FD&C Act provides a specific mechanism, called a "clinical hold," for prohibiting sponsors of clinical investigations from conducting the investigation.[75] FDA's implementing regulations in 21 CFR 312.42 identify the circumstances that may justify a clinical hold. In this section of this letter, we explain why FDA is not granting Petitioner's request to place all planned or ongoing studies of COVID-19 vaccines that include pregnant or pediatric subjects, including those that do not specifically exclude pregnant or pediatric individuals, on clinical hold under 21 CFR 312.42(b).

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

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

  FDA continues to evaluate all available information and, based on this evaluation and the currently available information, FDA does not believe that human subjects in any ongoing COVID-19 vaccine clinical trial under IND including pediatric or pregnant subjects (including those that do not specifically exclude pregnant or pediatric individuals) are or would be exposed to an unreasonable and significant risk of illness or injury. The Agency reviews the protocols for COVID-19 vaccine clinical trials proposing to enroll pediatric and pregnant subjects when they are submitted to the IND, in addition to any subsequent protocol amendments. For those ongoing clinical trials that have proceeded to studying COVID-19 vaccines in pediatric and pregnant populations, FDA has determined that, based on all information currently available to FDA, the studies do not expose subjects to unreasonable and significant risks. As noted, Petitioner refers to risks of anaphylaxis, myocarditis, and pericarditis. In addition, Petitioner asserts that COVID-19 "rarely manifests as severe disease in children, the infection fatality rate (IFR) 'near zero.'" However, as discussed above in section III.A., over 800 deaths have occurred in the pediatric age group 5 through 17 years of age. Additionally, Petitioner presents no new information pertaining to these topics (i.e., the risks associated with COVID-19 vaccines or COVID-19

[75] Section 505(i)(3) of the FD&C Act.

disease severity in children) and nothing indicating that human subjects in any COVID-19 study that includes pediatric or pregnant subjects (including those that do not specifically exclude pregnant or pediatric individuals) are or would be exposed to an unreasonable and significant risk of illness or injury.

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

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

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

  The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that the investigator brochures for any ongoing COVID-19 vaccine clinical trial under IND including pediatric or pregnant subjects (including those that do not specifically exclude pregnant or pediatric individuals) are misleading, erroneous, or materially incomplete.

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

  For ongoing COVID-19 vaccine clinical trials under IND that include pediatric or pregnant subjects (including those that do not specifically exclude pregnant or pediatric individuals), the Petitioner has not provided evidence and FDA is currently aware of no other information indicating that the INDs contain insufficient information required under 21 CFR 312.23 to assess the risks to subjects participating in the studies.

  With respect to the assertion regarding "Research involving pregnant women or fetuses" that "[p]er current Fact Sheets/Package Insert, for each vaccine, only a single rat or rabbit developmental toxicity study has been performed," we note that as a general matter, clinical trials of vaccines in pregnant women may proceed when adequate nonclinical studies, including reproductive and development toxicity studies in animal models, are conducted and safety and immunogenicity data for the vaccine are available from early Phase 1 and 2 clinical studies conducted in nonpregnant individuals.[76] As noted above more

[76] In this regard, FDA has sets forth recommendations for assessing the developmental toxicity potential of preventive vaccines for infectious diseases for females of childbearing potential and pregnant women. See

generally, Petitioner has not provided evidence and FDA is currently aware of no other information indicating that any INDs for ongoing COVID-19 vaccine clinical trials that include pediatric or pregnant subjects (including those that do not specifically exclude pregnant or pediatric individuals) contain insufficient information required under 21 CFR 312.23 to assess the risks to subjects participating in the studies.

- 21 CFR 312.42(b)(1)(v) [provides, in part, that]: The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (*i.e.*, affecting reproductive organs) or developmental toxicity (*i.e.*, affecting potential offspring)…

  Petitioner has not provided evidence and FDA is currently aware of no other information indicating that any ongoing COVID-19 vaccine clinical trials under IND including pediatric or pregnant subjects (including those that do not specifically exclude pregnant or pediatric individuals) are excluding from eligibility men or women with reproductive potential.

- 21 CFR 312.42(b)(2)(ii): The plan or protocol for the Phase 2 or Phase 3 investigation is clearly deficient in design to meet its stated objectives.

  The Agency reviewed the protocols for the ongoing COVID-19 vaccine investigations under IND including pediatric or pregnant subjects (including those that do not specifically exclude pregnant or pediatric individuals) at the time they were submitted to the INDs, as well as any subsequent amendments as they were submitted, and has determined that the study designs meet their stated objectives.

  At this time, the Agency is aware of no information to indicate that the protocols for any ongoing COVID-19 vaccine clinical trials under IND including pediatric or pregnant subjects (including those that do not specifically exclude pregnant or pediatric individuals) are clearly deficient in design to meet their stated objectives.

We note that the discussion above focuses on ongoing COVID-19 vaccine clinical trials under IND. For planned COVID-19 vaccine clinical trials that include pregnant or pediatric subjects, including those that do not specifically exclude pregnant or pediatric individuals, FDA will continue to evaluate each IND individually in accordance with applicable regulations.

FDA has reviewed the issues raised by the Petitioner relating to the request to "[i]mmediately suspend all ongoing clinical trials for all pediatric and pregnant subpopulations" and to "[a]dd pregnancy and pediatric exclusion criteria for all ongoing or planned Covid-19 vaccine clinical

Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications; Guidance for Industry (February 2006), https://www.fda.gov/media/73986/download.

trials."[77] For the reasons outlined above, and in light of information currently available to FDA, FDA has determined that grounds do not exist to grant those requests.

IV. CONCLUSION

FDA has considered Petitioner's requests as they relate to authorized and approved COVID-19 vaccines, as well as clinical trials for COVID-19 vaccines. For the reasons given in this letter, FDA denies the requests and therefore denies the Petition in its entirety.

Sincerely,

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

cc: Dockets Management Staff

[77] Petition at 1.