August 30, 2022

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Re: Citizen Petition (Docket Number: FDA-2022-P-1471)

Dear Mr. Howard,

This letter responds to the citizen petition (the Petition) dated July 1, 2022 that you (Petitioner) submitted to the Food and Drug Administration (FDA, the Agency, we) on behalf of Dr. Naomi Wolf, Daily Clout, and the Health Freedom Defense Fund requesting that FDA "revoke or suspend" the June 17, 2022 Emergency Use Authorizations (EUAs) for certain vaccines to prevent the Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in young children.

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 action. In accordance with Title 21 Code of Federal Regulations (CFR) 10.30(e)(3), and for the reasons stated below, FDA is denying the Petition.

Here is an outline of FDA's response:

I. Background

There is currently a pandemic of respiratory disease, COVID-19, caused by a novel coronavirus, SARS-CoV-2. The COVID-19 pandemic presents an extraordinary challenge to global health. On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19.[1] On February 4, 2020, pursuant to section 564 of the Federal Food, Drug, and Cosmetic Act (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.[2] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic ("COVID-19 EUA Declaration"), pursuant to section 564(b)(1) of the FD&C Act.[3] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[4]

Commercial vaccine manufacturers and other entities have developed and are developing COVID-19 vaccines, and clinical studies of these vaccines are underway and/or have been publicly reported. Between December 11, 2020 and July 13, 2022, FDA issued EUAs for four vaccines to prevent COVID-19, including vaccines sponsored by Pfizer Inc. (Pfizer),[5] ModernaTX, Inc. (Moderna),[6] Novavax Inc. (Novavax), and Janssen BioTech, Inc. (Janssen). The EUAs have been amended since initial issuance. For example, on June 17, 2022, the FDA authorized emergency use of the Pfizer-BioNTech COVID-19 Vaccine and the Moderna

[1] 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.
[2] HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[3] HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.
[4] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak, issued March 13, 2020, https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.
[5] Hereinafter "Pfizer-BioNTech COVID-19 Vaccine".
[6] Hereinafter "Moderna COVID-19 Vaccine".

COVID-19 Vaccine for the prevention of COVID-19 to include use in children down to 6 months of age. For the Pfizer-BioNTech COVID-19 Vaccine, FDA amended the EUA to include use of the vaccine in individuals 6 months through 4 years of age.[7] The vaccine had been authorized for use in individuals 5 years of age and older. For the Moderna COVID-19 Vaccine, FDA amended the EUA to include use of the vaccine in individuals 6 months through 17 years of age.[8] The vaccine had been authorized for use in individuals 18 years of age and older.

On August 23, 2021, the Agency approved the Biologics License Application (BLA) for Comirnaty (COVID-19 Vaccine, mRNA), and the approval was granted to BioNTech Manufacturing GmbH.[9] Comirnaty is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. On January 31, 2022, the Agency approved the BLA for Spikevax (COVID-19 Vaccine, mRNA), and the approval was granted to ModernaTX, Inc. Spikevax is indicated for active immunization to prevent 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

FDA's investigational new drug process applies to the development of new drugs and biological products, including vaccines.[10] 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[11]) 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.

[7] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months Through 4 Years of Age (June 16, 2022), https://www.fda.gov/media/159393/download.
[8] FDA, Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months Through 17 Years of Age (June 16, 2022), https://www.fda.gov/media/159611/download.
[9] BioNTech Manufacturing GmbH is the biologics license holder for this vaccine, which is manufactured by Pfizer for BioNTech Manufacturing GmbH.
[10] See 21 CFR 312.2(a) (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).
[11] 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.

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.[12] The IND describes the proposed clinical study in detail and, among other things, helps protect the safety and rights of human subjects.[13] In addition to other information, an IND must contain information on clinical protocols and clinical investigators.[14] 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 the study by an institutional review board (IRB),[15] and to adhere to the IND 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.[16]

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

[12] See 21 CFR 312.20(a).
[13] 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. This draft guidance, when finalized, will represent the current thinking of the Agency on this topic.
[14] See, e.g., 21 CFR 312.23(a)(6).
[15] 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.
[16] 21 CFR 312.22(a).

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."[17]

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.[18]

B. Licensed Vaccines Are Safe, Pure, and Potent

FDA has a stringent regulatory process for licensing vaccines.[19,20] 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."[21] 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 representative sample(s) of the product and summaries of results of tests performed on the lot(s) represented by the sample.[22]

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 proposed

[17] 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.
[18] 21 CFR 312.42(a).
[19] 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.
[20] Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[21] Section 351(a)(2)(C)(i)(I) of the PHS Act.
[22] 21 CFR 601.2(a).

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 have been demonstrated.[23] 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."[24] 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.

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.[25] 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.[26]

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.

[23] FDA, Vaccines, last updated August 2022, https://www.fda.gov/vaccines-blood-biologics/vaccines.
[24] 21 CFR 601.2(d).
[25] 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.
[26] COVID-19 EUA Declaration.

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

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

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

Although EUAs are governed under a different statutory framework than BLAs, FDA has made clear that issuance of an EUA for a COVID-19 vaccine would require that the vaccine demonstrated clear and compelling safety and efficacy in a large, well-designed Phase 3 clinical trial. In the guidance document Emergency Use Authorization for Vaccines to Prevent COVID-19 (EUA Vaccine Guidance), FDA has provided recommendations that describe key information that would support issuance of an EUA for a vaccine to prevent COVID-19.[27] In the EUA Vaccine 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.[28] 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.[29]

A Phase 3 trial of a vaccine is generally a 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.[30] During the entire study, subjects will be monitored for safety events. If the evidence from the clinical trial meets the pre-

[27] Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry, March 2022, (EUA Vaccine Guidance), https://www.fda.gov/media/142749/download.
[28] Id. at 4.
[29] Id.
[30] Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry, June 2020, (Vaccine Development and Licensure Guidance), https://www.fda.gov/media/139638/download.

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.

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.[31]

D. FDA Periodically Reviews Authorizations and May Revise or Revoke an Emergency Use Authorization if the Issuance Criteria Are No Longer Met

An EUA will remain in effect until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products is terminated under section 564(b)(2) of the FD&C Act or the EUA is revoked under section 564(g) of the FD&C Act. Section 564(g) provides that "[t]he Secretary shall periodically review the circumstances and the appropriateness of an authorization" under section 564. In addition, section 564(g)(2) states the Secretary "may revise or revoke an authorization" if:

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

Consistent with these provisions and section 564(g)(1) of the FD&C Act, FDA periodically reviews the circumstances and appropriateness of an EUA and revises or revokes an EUA if the criteria in section 564(g)(2) are met and if certain circumstances exist.[32]

III. Discussion

The "action requested" section of the Petition refers to FDA's June 17, 2022, authorization of the Moderna COVID-19 Vaccine for use in individuals 6 months through 17 years of age and of the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 6 months through 4 years of age. Petitioner then requests that FDA "revoke this authorization, or at least suspend it so the FDA can properly consider the potential risks and rewards in injecting young kids with these experimental pharmaceuticals."[33]

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[31] Id.

[32] Emergency Use Authorization of Medical Products and Related Authorities; Guidance for Industry and Other Stakeholders, January 2017, (EUA Guidance), at 29, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities.

[33] Petition at 2.

We interpret this as a request for FDA to revoke[34] the EUA for the Moderna COVID-19 Vaccine for use in individuals 6 months through 17 years of age, and to revoke the EUA for the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 6 months through 4 years of age.[35] Below, we address Petitioner's request and the information submitted by Petitioner in support of this requested action.[36]

A. EUAs for the Pfizer-BioNTech and Moderna COVID-19 Vaccines

i. EUA for the Pfizer-BioNTech COVID-19 Vaccine

On December 11, 2020, FDA issued an EUA for emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age and older. The EUA was subsequently amended, including on May 10, 2021, when FDA authorized the emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 12 through 15 years of age. Most recently, on June 17, 2022, the EUA was amended to authorize the Pfizer-BioNTech COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months through 4 years of age.[37]

[34] In responding to the request in the Petition that FDA "revoke…or at least suspend" the referenced EUAs, this letter uses the terminology used in section 564 of the FD&C Act, which describes circumstances under which FDA may revise or revoke an EUA. See Petition at 2 and section 564(g)(2) of the FD&C Act. Because the Petition does not request a revision to the EUAs, this letter focuses on the grounds for revocation.

[35] In addition to requesting this action, we note that Petitioner raises other concerns in the Petition, including concerns relating to what Petitioner refers to as "FDA's rushed process" in authorizing vaccines and concerns regarding vaccine mandates (e.g., the Petition states that "many American institutions, from employers to schools, have issued vaccine mandates based solely on the FDA's authorization (and implied recommendation) of them"). Petition at 2 and 5. With regard to Petitioner's assertion of a "rushed approval process," we note that FDA's science-based decision-making process is designed to assure that any vaccine that is authorized or approved meets all relevant statutory requirements. With regard to vaccine mandates, we note that FDA does not mandate use of vaccines. Concerns about potential third party vaccine requirements are better directed to those parties.

[36] In addition to Petitioner's assertions discussed in more detail below, we note that Petitioner states the following: "The FDA's analysis of the safety and efficacy of the COVID shots for young children is also misleading. Three different Pfizer doses were given; 3 mcg for kids ages 5 through 11, 10 mcg for kids ages 12 through 17, and 30 mcg for those over 18. All Moderna recipients received 100 mcg. This means that a 12-year-old girl weighing 90-pounds got the same dosage as a 17- year-old, 200-pound male athlete, and that an 11-year-old on the last day of this 11th year would get a dose that would more than triple one day later, on his 12th birthday." Petition at 3. We disagree that the dosage of COVID-19 vaccines given to study participants indicates a misleading analysis by FDA, and Petitioner fails to explain any connection between such dosages and vaccine safety or efficacy. Accordingly, these assertions do not provide a reasonable basis for FDA to revoke the EUAs and are not further discussed in this letter.

[37] For a description of all revisions to the EUA for Pfizer-BioNTech COVID-19 vaccine, see Pfizer-BioNTech COVID-19 Vaccine Letter of Authorization (July 8, 2022), https://www.fda.gov/media/150386/download.

Currently, the Pfizer-BioNTech COVID-19 Vaccine[38] is authorized for emergency use as a:

- Three-dose primary series for individuals 6 months through 4 years of age.
- Two-dose primary series for individuals 5 years of age and older.
- Third primary series dose for individuals 5 years of age and older who have been determined to have certain kinds of immunocompromise.
- Single booster dose for individuals 5 through 11 years of age at least five months after completing a primary series of the Pfizer-BioNTech COVID-19 Vaccine.
- First booster dose for individuals 12 years of age and older at least five months after completing a primary series of the Pfizer-BioNTech COVID-19 Vaccine or Comirnaty vaccine.
- First booster dose for individuals 18 years of age and older who have completed primary vaccination with another authorized or approved COVID-19 vaccine. The dosing interval for this first booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.
- Second booster dose for individuals 50 years of age and older at least four months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine.
- Second booster dose for individuals 12 years of age and older with certain kinds of immunocompromise at least four months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine.

The Agency issued the EUA for Pfizer-BioNTech COVID-19 Vaccine after a thorough evaluation of scientific data regarding the safety, effectiveness, and manufacturing information (which helps ensure product quality and consistency) and after reaching a determination that the vaccine meets the statutory requirements under section 564 of the FD&C Act. This letter

[38] Comirnaty is the proprietary name for the product licensed under the BLA. The Pfizer-BioNTech COVID-19 Vaccine has been available since December 11, 2020, pursuant to EUA. The two approved formulations of Comirnaty are the same formulations, respectively, as the two FDA-authorized formulations of Pfizer-BioNTech COVID-19 Vaccine for individuals ≥12 years, and vials of the BLA-compliant vaccine may bear the name "Pfizer-BioNTech COVID-19 Vaccine." Because of these features, and because Comirnaty is commonly referred to as the "Pfizer vaccine" or the "Pfizer-BioNTech COVID-19 Vaccine," certain references in this section to "Pfizer-BioNTech COVID-19 Vaccine" may also be applicable to uses of Comirnaty that are authorized under EUA.

incorporates by reference the EUA Review Memoranda for the Pfizer-BioNTech COVID-19 Vaccine,[39] which discuss this determination, and the data upon which it was based, in detail.[40]

ii. EUA for the Moderna COVID-19 Vaccine

On December 18, 2020, FDA issued an EUA for emergency use of the Moderna COVID-19 Vaccine for the prevention of COVID-19 for individuals 18 years of age and older. The EUA was subsequently amended. Most recently, on June 17, 2022, the EUA was amended to authorize the use of the Moderna COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS- CoV-2 in individuals 6 months through 17 years of age.[41] Currently, the Moderna COVID-19 Vaccine[42] is authorized for emergency use as a:

- Two-dose primary series for individuals 6 months of age and older.
- Third primary series dose for individuals 6 months of age and older who have been determined to have certain kinds of immunocompromise.
- First booster dose for individuals 18 years of age and older at least five months after completing a primary series of the Moderna COVID-19 Vaccine or Spikevax vaccine.
- First booster dose for individuals 18 years of age and older who have completed primary vaccination with another authorized or approved COVID-19 vaccine. The dosing interval for this first booster dose is the same as that authorized for a booster dose of the vaccine used for primary vaccination.
- Second booster dose for individuals 50 years of age and older at least four months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine.
- Second booster dose for individuals 18 years of age and older with certain kinds of immunocompromise at least four months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine.

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[39] 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; January 6, 2022; March 28, 2022; May 17, 2022; and June 16, 2022 (referred to collectively in this response as "FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda"), available at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine.

[40] This letter incorporates by reference FDA's Summary Basis for Regulatory Action (SBRA) for Comirnaty, available at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine#comirnaty.

[41] For a description of all revisions to the EUA for Moderna COVID-19 Vaccine, see Moderna COVID-19 Vaccine Letter of Authorization (June 17, 2022), https://www.fda.gov/media/144636/download.

[42] Spikevax is the proprietary name for the product licensed under the BLA. The Moderna COVID-19 Vaccine has been available since December 18, 2020, pursuant to EUA. The approved formulation of Spikevax and the FDA-authorized Moderna COVID-19 Vaccine for providing the primary series in individuals ≥12 years are the same formulation. Because of these features, and because Spikevax may be commonly referred to as the "Moderna vaccine" or the "Moderna COVID-19 Vaccine," certain references in this section to "the Moderna COVID-19 Vaccine" may also be applicable to uses of Spikevax that are authorized under EUA.

The Agency issued the EUA for Moderna COVID-19 Vaccine after a thorough evaluation of scientific data regarding the safety, effectiveness, and manufacturing information and after reaching a determination that the vaccine meets the statutory requirements under section 564 of the FD&C Act. This letter incorporates by reference the EUA Review Memoranda for the Moderna COVID-19 Vaccine, which discuss this determination,[43] and the data upon which it was based, in detail.[44]

B. The Standard for Revocation of EUAs Is Not Met

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.[45] The verb "may" is ordinarily permissive, particularly when the statute elsewhere uses the term "shall" to confer a mandatory duty.[46] Further underscoring FDA's discretion, the EUA statute explicitly provides that all decisions regarding EUAs are "committed to agency discretion."[47]

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

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[43] FDA, Moderna COVID-19 Vaccine EUA Decision Memoranda and Addenda to Decision Memoranda, dated December 18, 2020; August 12, 2021; October 20, 2021; November 18, 2021; November 19, 2021; December 30, 2021; January 6, 2022; March 28, 2022; and June 16, 2022; (referred to collectively in this response as "FDA's Moderna COVID-19 Vaccine EUA Decision Memoranda and Addenda"), available at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/spikevax-and-moderna-covid-19-vaccine.

[44] This letter incorporates by reference FDA's Summary Basis for Regulatory Action (SBRA) for Spikevax, available at https://www.fda.gov/vaccines-blood-biologics/spikevax.

[45] Section 564(g)(2) of the FD&C Act (emphasis added).

[46] 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 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." .

[47] 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].").

circumstances,"[48] 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 EUA Guidance notes that once an EUA is issued for a product, in general, that EUA will remain in effect for the duration of the EUA declaration under which it was issued, "unless the EUA is revoked because the criteria for issuance . . . are no longer met or revocation is appropriate to protect public health or safety (section 564(f),(g) [of the FD&C Act])."[49] Thus, in this section, we assess whether any of the statutory conditions under which FDA may revoke an EUA are met, namely: (1) whether the circumstances described under section 564(b)(1) of the FD&C Act no longer exist, (2) whether the criteria for their issuance under section 564(c) of the FD&C Act are no longer met, and (3) whether other circumstances make a revision or revocation appropriate to protect the public health or safety.

i. Circumstances Described under 564(b)(1) Continue to Exist

Section 564(b)(1) of the FD&C Act describes the circumstances under which the HHS Secretary may declare that circumstances exist justifying the issuance of EUAs. As explained above, on February 4, 2020, pursuant to section 564(b)(1)(C) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of U.S. citizens living abroad, and that involves the virus that causes COVID-19.[50] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564(b)(1) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)).[51]

Based on this declaration and determination, under section 564(c) of the FD&C Act (21 U.S.C. § 360bbb-3(c)), FDA may issue an EUA during the COVID-19 pandemic after FDA concludes that the statutory requirements provided in section 564(c) are met. Section 564(b)(2) sets forth the statutory standard for termination of an EUA declaration. An EUA declaration remains in place until the earlier of: (1) a determination by the HHS Secretary that the circumstances that precipitated the declaration have ceased (after consultation as appropriate with the Secretary of Defense) or (2) a change in the approval status of the product such that the authorized use(s) of the product are no longer unapproved.

The Petition does not demonstrate, nor does the Petition assert any claim(s), that the circumstances described under section 564(b)(1) no longer exist. The Petition therefore has not shown that there are grounds for revoking the EUA for the Moderna COVID-19 Vaccine for use in individuals 6 months through 17 years of age, or for revoking the EUA for the Pfizer-

[48] 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).
[49] EUA Guidance at 28.
[50] 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.
[51] COVID-19 EUA Declaration.

BioNTech COVID-19 Vaccine for use in individuals 6 months through 4 years of age, on the basis of section 564(g)(2)(A) (i.e., on the basis that the circumstances described under section 564(b)(1) no longer exist).

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

Section 564(g)(2)(B) of the FD&C Act provides that FDA may revise or revoke an authorization if the criteria for issuance of the authorization under section 564(c) of the FD&C Act are no longer met. This section describes why the Petition has not demonstrated that the criteria under section 564(c) of the FD&C Act are no longer met with respect to the Pfizer-BioNTech COVID-19 Vaccine for use in individuals ages 6 months through 4 years and with respect to the Moderna COVID-19 Vaccine for use in individuals ages 6 months through 17 years and why, therefore, FDA is not revoking the EUAs for the Pfizer-BioNTech and Moderna COVID-19 Vaccines for use in these populations under the authority in section 564(g)(2)(B) of the FD&C Act.

1. Serious or Life-Threatening Disease or Condition

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

The SARS-CoV-2 pandemic continues to present an extraordinary challenge to global health and, as of August 17, 2022, has caused more than 593 million cases of COVID-19 and claimed the lives of more than 6.4 million people worldwide.[52] In the U.S., as of August 17, 2022, more than 93 million cases and over 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).[53] On January 31, 2020, the 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-CoV-2 virus and COVID-19 pandemic may be found in FDA's decision memoranda regarding the Pfizer-BioNTech COVID-19 Vaccine EUA and the Moderna COVID-19 Vaccine EUA.[54]

The Petition states "we know that COVID-19 poses minimal risk to young people."[55] To the extent this constitutes an argument that SARS-CoV-2 cannot cause a serious or life-threatening disease or condition in this age population, FDA disagrees.

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[52] Johns Hopkins University School of Medicine, Coronavirus Resource Center, https://coronavirus.jhu.edu/map.html (accessed August 18, 2022).
[53] CDC, COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#datatracker-home (accessed August 18, 2022).
[54] See FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda and FDA's Moderna COVID-19 Vaccine EUA Decision Memoranda and Addenda.
[55] Petition at 5. We note that the statutory criterion under section 564(c)(1) of the FD&C Act does not require a conclusion that the agent referred to in an EUA declaration can cause a serious or life-threatening disease or

With respect to the impact of the SARS-CoV-2 pandemic on individuals within the age groups at issue in Petitioner's request, as of August 17, 2022, approximately 14.6 million COVID-19 cases in individuals 0-17 years of age have been reported to the CDC.[56] Some of these cases have resulted in hospitalization and death. The cumulative rate of COVID-19 associated hospitalization was 270.3 per 100,000 for the 0-4 years of age population and 106.9 per 100,000 for the 5-17 years of age populations as of the week ending August 6, 2022 based on COVID-NET data reported to the CDC.[57] As of August 17, 2022, 546 deaths associated with COVID-19 have been reported among individuals 0 through 4 years of age, 431 deaths reported among individuals ages 5 through 11, 437 deaths reported among individuals ages 12 through 15, and 333 deaths reported among individuals 16 through 17.[58,59] It is difficult to estimate the incidence of COVID-19 among children and adolescents because they are frequently asymptomatic and infrequently tested; there may also be underreporting of COVID-19 due to the availability and use of at-home tests.[60]

While it has largely been the case that COVID-19 tends to be less severe in children and adolescents than adults, the Omicron wave has seen more of these individuals getting sick with

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condition in a specific age group. Regardless, FDA concludes that SARS-CoV-2 can cause a serious or life-threatening disease or condition in individuals 6 months through 17 years of age.

[56] CDC, Demographic Trends of COVID-19 cases and deaths in the US reported to CDC, https://covid.cdc.gov/covid-data-tracker/#demographics (accessed August 18, 2022).

[57] CDC, COVID-NET Laboratory-confirmed COVID-19 hospitalizations, https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network (accessed August 18, 2022). The current network covers nearly 100 counties.

[58] CDC, Demographic Trends of COVID-19 cases and deaths in the US reported to CDC, https://covid.cdc.gov/covid-data-tracker/#demographics (accessed August 18, 2022).

[59] Petitioner cites to an article from Reuters (CDC Reports Fewer COVID-19 Pediatric Deaths After Data Correction, (March 18, 2022), https://www.reuters.com/business/healthcare-pharmaceuticals/cdc-reports-fewer-covid-19-pediatric-deaths-after-data-correction-2022-03-18/) in support of Petitioner's assertion that statistics on COVID-related pediatric deaths "may be inflated." Petition at 5. Additionally, Petitioner states that the aforementioned article "note[s] that while children accounted for 19 percent of COVID infections, they only accounted for 0.26 percent of deaths." Petition at 5. To clarify, the referenced article states, "Children accounted for about 19% of all COVID-19 cases, but less than 0.26% of cases resulted in death, according to the American Academy of Pediatrics, which summarizes state-based data." Petitioner also asserts that, according to data from UNICEF individuals under the age of 20 "accounted for fewer than 0.4 percent of global COVID deaths." Petition at 5. Petitioner appears to be citing these data to support the Petition's assertion that COVID-19 "poses minimal risk to young people" while simultaneously making assertions that data may be inflated. Petition at 5. While questions or requests about CDC data should be directed to CDC, we note that the CDC website provides information about data sources—including the limitations of those data sources—for its reported COVID-19-associated death and hospitalization numbers. See, e.g., CDC, Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET), https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html (last updated Aug. 4, 2022); CDC, About CDC COVID-19 Data, https://www.cdc.gov/coronavirus/2019-ncov/covid-data/about-us-cases-deaths.html (last updated June 17, 2022). The Petition provides no new information about the limitations of CDC COVID-19 data sources. Additionally, the data cited in the Petition does not alter the conclusion that SARS-CoV-2 can cause a serious or life-threatening disease or condition in individuals 6 months through 17 years of age.

[60] See Rader, et al., Use of At-Home COVID-19 Tests — United States, August 23, 2021–March 12, 2022, Morb Mortal Wkly Rep. (Apr. 1, 2022),71: 489–94, DOI: http://dx.doi.org/10.15585/mmwr.mm7113e1 ("Mandated COVID-19 reporting requirements omit at-home tests, and there are no standard processes for test takers or manufacturers to share results with appropriate health officials. Therefore, with increased COVID-19 at-home test use, laboratory-based reporting systems might increasingly underreport the actual incidence of infection.").

the disease and being hospitalized; children and adolescents may also experience longer term effects, even following initially mild disease. However, as with adults, children and adolescents with underlying conditions such as asthma, chronic lung disease, and cancer are at higher risk than their heathier counterparts for COVID-19-related hospitalization and death. Of the children who have developed severe 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 August 1, 2022, the CDC received reports of 8,798 cases and 71 deaths that met the definition for MIS-C.[61]

As explained above, FDA has concluded that SARS-CoV-2 can cause a serious or life-threatening disease or condition. Petitioner has not provided any data, and FDA is not aware of any data, that change the conclusion that SARS-CoV-2 can cause a serious or life-threatening disease or condition, including in individuals 6 months to 17 years of age. The Petition thus fails to establish that the criterion under section 564(c)(1) is no longer met for the Pfizer-BioNTech and Moderna COVID-19 Vaccines for use in the populations at issue in Petitioner's request.

2. Evidence of Effectiveness

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

FDA 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, when administered as a 3-dose primary series to individuals 6 months through 4 years of age, may be effective to prevent COVID-19. Likewise, FDA has also 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 Moderna COVID-19 Vaccine, when administered as a 2-dose primary series to individuals 6 months through 17 years of age, may be effective to prevent COVID-19. The basis for these determinations are explained in detail in FDA's decision memoranda regarding the Pfizer-BioNTech[62] and the Moderna[63] COVID-19 Vaccine EUAs.

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[61] 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 August 18, 2022).
[62] See FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 4 Years of Age (June 16, 2022), https://www.fda.gov/media/159393/download.
[63] See FDA, Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 17 Years of Age (June 16, 2022), https://www.fda.gov/media/159611/download.

Petitioner raises concerns about the effectiveness of the Pfizer-BioNTech and Moderna COVID-19 Vaccines and also about the adequacy of clinical data relied upon to authorize these vaccines for emergency use in children.[64] In this section, we address these arguments and explain why they do not alter the Agency's determination that the criterion in section 564(c)(2)(A) is satisfied.

a. Petitioner's Claims Regarding the Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine

On June 17, 2022, FDA authorized the emergency use of Pfizer-BioNTech COVID-19 Vaccine in individuals 6 months through 4 years of age in response to an EUA amendment request that included safety and effectiveness data from the ongoing Phase 2/3 randomized, double-blinded and placebo-controlled trial of the Pfizer-BioNTech COVID-19 Vaccine in 1,178 Pfizer-BioNTech COVID-19 Vaccine recipients and 598 placebo recipients 6 months through 23 months of age; and 1,835 Pfizer-BioNTech COVID-19 Vaccine recipients and 915 placebo recipients 2 years through 4 years of age who received at least one dose of the investigational product (Study C4591007).[65] We therefore interpret Petitioner's arguments concerning clinical trial data for the Pfizer-BioNTech COVID-19 Vaccine to be in reference to this study.

Petitioner makes several assertions relating to the quantity of COVID-19 cases in this study. Specifically, Petitioner asserts that "Pfizer's own clinical trial data found more COVID-19 cases in children who received the shot than those who received the placebo."[66] Additionally, Petitioner states that, "of the 47 children diagnosed with COVID during the three weeks between the first and second doses, 34 were vaccinated."[67] Petitioner asserts that "[b]oth Pfizer and FDA ignored this data" and that "Pfizer disregarded 97 percent of COVID illnesses that occurred during the trial, ultimately concluding that only three children from the vaccinated group contracted COVID-19 compared to seven children in the placebo group."[68]

Petitioner's assertions with respect to the quantity of COVID-19 cases in the Pfizer-BioNTech COVID-19 Vaccine study do not represent new information or data that would change FDA's conclusion based on the totality of scientific evidence available that the Pfizer-BioNTech

[64] In addition to making assertions specific to the Pfizer-BioNTech and Moderna COVID-19 Vaccines, we note that Petitioner also asserts more generally that "data from around the world show that hospitalizations and deaths are occurring primarily in the vaccinated." Petition at 5. Petitioner further asserts that "Portugal has the highest vaccination rate of any country in Europe aside from…Malta…[y]et, Portugal now has the highest case and COVID death rate per capita in Europe and the second highest COVID fatality rate in the world behind Taiwan, according to Our World in Data." Petition at 5. Petitioner does not provide any further reference or citation to support these assertions. Furthermore, Petitioner does not assert or provide evidence of any connection between these assertions and the Pfizer-BioNTech or Moderna COVID-19 Vaccines. Thus, Petitioner's assertions regarding COVID-19 infection and fatality rates in other countries do not provide a reasonable basis for FDA to change its conclusions with respect to the effectiveness of the Pfizer-BioNTech and Moderna COVID-19 Vaccines.

[65] Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 4 Years of Age, at 6.

[66] Petition at 3.

[67] Id.

[68] Id. at 3-4.

COVID-19 Vaccine, when administered as a 3-dose primary series to individuals 6 months through 4 years of age, may be effective to prevent COVID-19.

In Study C4591007, participants 6 months through 4 years of age were randomized 2:1 to receive 2 doses of either the Pfizer-BioNTech COVID-19 Vaccine (3 µg mRNA per dose) or saline placebo, administered 3 weeks apart.[69] Following analysis of the post-Dose 2 safety and effectiveness data, the protocol was amended to administer a third primary series dose to participants 6 months through 4 years of age at least 8 weeks after Dose 2.[70]

The study was designed to demonstrate effectiveness through immunobridging. SARS-CoV-2 neutralizing antibody titers (NT50, SARS-CoV-2 mNG microneutralization assay) in study participants were compared to a subset of participants (16 through 25 years of age) who had been vaccinated in clinical efficacy study C4591001.[71] Authorization was based on the results of a comparison of immune responses following three doses of the Pfizer-BioNTech COVID-19 Vaccine (3 µg mRNA per dose) in each of two age groups of children (6 through 23 months of age; 2 through 4 years of age) to the immune responses of individuals 16 through 25 years of age who received two doses of the Pfizer-BioNTech COVID-19 Vaccine (30 µg mRNA per dose) in Study C4591001.[72] The immune responses to the vaccine of approximately 80 children 6 through 23 months of age and approximately 140 children 2 through 4 years of age were compared to the immune response of approximately 170 vaccine recipients 16 through 25 years of age.[73] In these analyses, the immune response to the vaccine for both age groups of children was comparable to the immune response of the older participants and met the prespecified immunobridging success criteria.

As a general matter, in assessing benefits for particular populations, FDA is not limited to considering evidence of effectiveness based on clinical trials with disease endpoints. In some cases, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults.[74] In addition, a study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group.[75] 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.

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[69] Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 4 Years of Age, at 6.
[70] Id.
[71] Id. at 18.
[72] Id. at 6, 20-22.
[73] Id. at 32-34.
[74] 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").
[75] 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").

FDA has explained that regulatory precedent with other preventive vaccines provides a basis for inference of vaccine effectiveness in pediatric populations based on immunobridging to an adult population in which clinical disease endpoint vaccine efficacy has been demonstrated for the same prototype vaccine. The immune marker(s) used for immunobridging do not need to be scientifically established to predict protection but should be clinically relevant to the disease.[76] Based on available data in humans and animal models, FDA considers neutralizing antibody titers (a functional measure of the vaccine immune response against SARS-CoV-2) to be clinically relevant for immunobridging to infer effectiveness of COVID-19 vaccines in pediatric age groups. As FDA acknowledged at the time of its June 17, 2022 decision, no specific neutralizing antibody titer has been established to predict protection against COVID-19.[77] Because of this, we considered two immunogenicity endpoints (geometric mean titer [GMT] and seroresponse rate) appropriate for comparing the range of neutralizing antibody responses elicited by the vaccine in pediatric vs. young adult populations.

As discussed, in Study C4591007, vaccine effectiveness in individuals 6 months through 4 years of age was inferred by immunobridging. We note that preliminary descriptive analyses of vaccine efficacy (VE) were also provided. The descriptive analyses included COVID-19 cases occurring at least 7 days after completion of the 3 dose primary series. These analyses included participants with and without evidence of SARS-CoV-2 infection prior to 7 days after Dose 3 ("Dose 3 evaluable efficacy population").[78] Three COVID-19 cases occurred in participants 6-23 months of age, with 1 COVID-19 case in the vaccinated group compared to 2 in the placebo group, corresponding to an estimated VE of 75.6% (95% CI: −369.1%, 99.6%), and 7 COVID-19 cases occurred in participants 2-4 years of age, with 2 cases in the vaccinated group and 5 in the placebo group, corresponding to an estimated VE of 82.4% (95% CI: −7.6%, 98.3%).[79] FDA's assessment of these analyses determined that there were too few cases of COVID-19 in the clinical trial participants to reliably estimate the effectiveness of the 3-dose series in children 6 months through 23 months and 2 through 4 years of age.[80]

Additionally, we note that—contrary to the Petitioner's assertion that cases of COVID-19 that occurred during the trial were "ignored" —FDA conducted post-hoc analyses of VE for all participants regardless of evidence of prior infection at selected time points during and following completion of the primary series.[81]

Petitioner's assertions relating to the quantity of COVID-19 cases in the Pfizer-BioNTech COVID-19 Vaccine study do not alter FDA's conclusion, based on the totality of scientific

[76] See FDA, Vaccines and Related Biological Products Advisory Committee Meeting June 10, 2021 FDA Briefing Document at 9-11, available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-10-2021-meeting-announcement#event-materials; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 4 Years of Age, at 16.
[77] Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 4 Years of Age, at 16.
[78] Id. at 7, 57.
[79] Id. at 57.
[80] Id. at 7, 57.
[81] Id. at 39-41.

evidence available, that the Pfizer-BioNTech COVID-19 Vaccine, when administered as a 3-dose primary series to individuals 6 months through 4 years of age, may be effective to prevent COVID-19.

In addition, Petitioner makes assertions relating to COVID-19 severity during Study C4591007. Petitioner states that 6 children between the ages of 2 and 4 of the vaccine group developed severe COVID symptoms, while only 1 child in the placebo group developed such symptoms. Petitioner claims that these statistics suggest "that the shot does not reduce the chances of developing severe COVID—and may in fact cause it."[82]

In Study C4591007 the case definition for a severe COVID-19 case included a confirmed COVID-19 case with at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR and HR, by age, 1 SpO2≤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 (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 ICU; or
- Death.[83]

Regarding the results referenced by Petitioner, 5 of the 6 reported severe COVID-19 cases in the vaccine group met criteria for a severe case based on 1 criterion: increased heart rate (n=2) or increased respiratory rate (n=3), all of which were considered by the investigator as not clinically significant based on examination at the illness visit and contributing circumstances such as the participant crying during examination.[84] The final severe COVID-19 case in the vaccine group occurred 99 days post-Dose 2 in a 2-year-old participant who had increased respiratory rate (RR) and decreased SpO2 as severe case criteria and was hospitalized due to COVID-19.[85] All cases occurred post-Dose 2 (range 32-208 days post-Dose 2), and none occurred post-Dose 3.[86] Although there is an imbalance in the number of cases of COVID-19 that met the protocol definition for severe COVID-19, all but one of these cases in the vaccine group were considered not clinically significant and all occurred before the third dose. The totality of the scientific evidence available supports the conclusion that the Pfizer-BioNTech COVID-19 Vaccine, when

[82] Petition at 3.
[83] Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 4 Years of Age, at 74.
[84] Id. at 39.
[85] Id.
[86] Id.

administered as a 3-dose primary series to individuals 6 months through 4 years of age, may be effective to prevent COVID-19.

Petitioner has not provided any data in the Petition, and FDA is not aware of any data, that change FDA's conclusion that the Pfizer-BioNTech COVID-19 Vaccine, when administered as a 3-dose primary series to individuals 6 months through 4 years of age, may be effective to prevent COVID-19. The criterion under section 564(c)(2)(A) of the FD&C Act continues to be met.

b. Petitioner's Claims Regarding the Effectiveness of the Moderna COVID-19 Vaccine

Referencing the aforementioned issues raised by Petitioner in regard to the Pfizer-BioNTech COVID-19 Vaccine, Petitioner asserts "[t]here are similar flaws in the Moderna data."[87] However, Petitioner does not present any new data or information to support this assertion, but instead references the following conclusory statements regarding the Moderna COVID-19 Vaccine from a document published online:

> Efficacy? Middling at best, even in a very short window after the second shot.
>
> How about stopping transmission via reducing asymptomatic infections? Nope.
>
> Helpful in the one high risk group for which the study gathered data, obese infants? Negative efficacy.
>
> And, of course, while we expect at least moderate reduction in Covid-19 hospitalizations, the study was too small and brief to find any severe infections in either placebo or vaccine group. So, no data there.[88]

The referenced document appears to be an opinion piece that does not present any new data or information regarding the Moderna COVID-19 Vaccine that is of the scientific quality that FDA would consider in making regulatory decisions pertaining to the safety and effectiveness of a vaccine.

On June 17, 2022, FDA authorized the emergency use of the Moderna COVID-19 Vaccine for use in individuals 6 months through 17 years of age in response to an EUA amendment request submitted by Moderna.[89] The EUA amendment request included safety and effectiveness data from two ongoing Phase 2/3 randomized, double-blinded and placebo-controlled trials (Studies P203 and P204) of the Moderna COVID-19 Vaccine that included approximately 14,000 participants 6 months through 17 years of age enrolled at sites in the United States and Canada,

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[87] Petition at 4.

[88] Id. quoting: Hollander, The "Safe and Effective" Moderna Covid Vaccine for Infants Might be Neither (June 29, 2022), https://doctorbuzz.substack.com/p/the-safe-and-effective-moderna-covid.

[89] See Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 17 Years of Age.

including 10,285 participants who received at least one dose of Moderna COVID-19 Vaccine.[90] Study P203 included participants 12-17 years of age. Study P204 included participants in three pediatric age cohorts: 6-23 months of age, 2-5 years of age, and 6-11 years of age.[91] Vaccine effectiveness for all four pediatric age cohorts was inferred by immunobridging based on a comparison of SARS-CoV-2 neutralizing antibody (nAb) responses at 1 month after Dose 2 in participants in each age cohort to the nAb responses generated by young adults 18-25 years of age, the most clinically relevant subgroup of the adult study population for whom VE was demonstrated in a clinical endpoint efficacy trial.[92] Immunobridging success criteria were met for all four pediatric age cohorts.[93]

As noted, 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 Moderna COVID-19 Vaccine, when administered as a 2-dose primary series to individuals 6 months through 17 years of age, may be effective to prevent COVID-19. The basis for this determination is explained in detail in FDA's decision memorandum. FDA is not aware of any data that change this conclusion, nor has Petitioner provided any such data in the Petition. The criterion under section 564(c)(2)(A) of the FD&C Act continues to be met.

3. Benefit-Risk Analysis

Section 564(c)(2)(B) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude that "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." FDA authorized the Pfizer-BioNTech COVID-19 Vaccine for emergency use in individuals 6 months through 4 years of age, and the Moderna COVID-19 Vaccine for emergency use in individuals 6 months through 17 years of age, after reaching a determination that, among other things, the known and potential benefits of these vaccines, when used to prevent COVID-19 in these populations, outweigh their known and potential risks.[94]

Petitioner asserts that "there is significant evidence that the COVID-19 shots . . . have serious known and unknown harms."[95] In this section, we address Petitioner's arguments relevant to the risks and benefits of the Pfizer-BioNTech and Moderna COVID-19 Vaccines and explain why they do not alter the Agency's determination that the criterion in section 564(c)(2)(B) is satisfied. For the reasons discussed in this section, the criterion under section 564(c)(2)(B) of the FD&C Act continues to be met.

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[90] Id. at 10.
[91] Id.
[92] Id. at 10-11, 181-182.
[93] Id.
[94] For an extensive discussion of FDA's analysis of the clinical trial data regarding the risks and benefits of these vaccines, see FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda and FDA's Moderna COVID-19 Vaccine EUA Decision Memoranda and Addenda.
[95] Petition at 5.

a. Petitioner's Statement Regarding Deaths and a "[F]lood of [A]dverse [E]vents"

Petitioner claims that "[m]ore than three percent of the subjects died during the trials and there was such a flood of adverse events that Pfizer had to hire 2,400 full-time employees to handle the paperwork."[96] Petitioner does not provide any reference or additional information in support of these claims. Based on the data submitted in support of the June 17, 2022 EUA amendments, there were no deaths reported in Pfizer-BioNTech COVID-19 Vaccine Study C4591007 in participants 6 months through 4 years of age and no deaths reported in Moderna COVID-19 Vaccine Studies P203 and P204 among participants 6 months through 17 years of age.[97]

FDA finds no basis in Petitioner's unsupported statement to change its conclusions that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks when used to prevent COVID-19 in individuals 6 months through 4 years of age, and that the known and potential benefits of the Moderna COVID-19 Vaccine outweigh the known and potential risks when used to prevent COVID-19 in individuals 6 months through 17 years of age.

b. Petitioner's Reference to the Size of the Pfizer-BioNTech COVID-19 Vaccine Study

The Petition characterizes the Pfizer-BioNTech COVID-19 Vaccine study as "small" and asserts that "there is even less evidence about the potential risks of Pfizer's shot in young kids" (as compared to the Moderna COVID-19 Vaccine) given the size.[98] To the extent Petitioner is suggesting the size of Study C4591007 was insufficient to allow for an adequate assessment of the known and potential risks of the Pfizer-BioNTech COVID-19 Vaccine, we disagree.

In reviewing the EUA amendment request, FDA found that Study C4591007 was of sufficient size and that it was adequately powered to support the agency's determination, based on the totality of the scientific evidence available, that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks for individuals 6 months through 4 years of age. Petitioner has provided no information regarding the size of Study C4591007 that alters this determination. The Petition has not shown that the trial was too small to generate relevant safety information, such that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine do not outweigh the known and potential risks when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months through 4 years of age.

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[96] Id at 3. FDA notes that the hiring practices of a company are not relevant to whether the criteria under section 564(c) of the FD&C Act are no longer met.

[97] See Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 4 Years of Age; Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 17 Years of Age.

[98] Petition at 4.

c. Petitioner's Statements Regarding Completion of the Pfizer-BioNTech COVID-19 Vaccine Study

Petitioner states that "4,526 children enrolled in the Pfizer trial but roughly 3,000 did not finish it."[99] Petitioner then asks "[c]ould it be that those 3,000 children who received the shot suffered such severe adverse reactions to the shots that their parents removed them from the trial" and "[d]id FDA follow up to ascertain the reasons for 3,000 sets of parents removing their children?"[100]

Study C4591007 is ongoing, thus at the time of the data cut off not all subjects had received a third vaccine dose. As discussed above in Section III.B.ii.2.a, the Phase 2/3 Study Design of Study C4591007 included a total of 4,526 participants 6 months through 4 years of age who were randomized 2:1 to receive two doses of vaccine or placebo, 3 weeks apart (number of participants 6-23 months of age: 1,178 vaccine, 598 placebo; number of participants 2-4 years of age: 1,835 vaccine, 915 placebo).[101] Based on analyses of post-Dose 2 safety and effectiveness data, the protocol was amended to add a third primary series dose at least 8 weeks after Dose 2.[102] Participants enrolled prior to implementation of this protocol amendment (N=3,883; February 1, 2022), were able to be unblinded at their 6-month post-Dose 2 visit, and those originally randomized to placebo were offered vaccination at the age-appropriate dose level. Participants enrolled after implementation of this protocol amendment would be unblinded at their 6-month post Dose 3 visit, and those originally randomized to placebo would be offered vaccination.[103] At the time of the data cut off, the safety population included participants in the blinded and unblinded parts of the study: of the 1,178 vaccine recipients 6-23 months of age, 386 (32.8%) had received 3 vaccine doses.[104] Of the 1,835 vaccine recipients 2-4 years of age, 606 (33.0%) had received 3 vaccine doses.[105] Contrary to the petitioners' assertion that "roughly 3000 children did not finish [the study]" subjects who did not receive the third dose did not necessarily withdraw from the study[106], but because the study is ongoing many subjects had not received the third dose at the time of the data cut-off.

FDA finds no basis in Petitioner's statements regarding completion of the Pfizer-BioNTech COVID-19 Vaccine study to change its conclusion that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks when used to prevent COVID-19 in individuals 6 months through 4 years of age.

[99] Id. at 3.
[100] Id.
[101] Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 4 Years of Age, at 6.
[102] Id. at 17.
[103] Id.
[104] Id. at 22-23.
[105] Id. at 23-24
[106] Id. at 25-28.

d. Petitioner's Reference to Risk of Myocarditis

Petitioner also states that "there is the known risk of myocarditis, especially in young men, which has been documented by governments across the globe."[107] FDA has carefully considered the risks of myocarditis and pericarditis for vaccine recipients and has concluded that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine outweigh their known and potential risks in the age groups at issue in Petitioner's request.[108] In addition, we note that for both the Pfizer-BioNTech COVID-19 Vaccine and the Moderna COVID-19 Vaccine, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) includes a warning about the risks of myocarditis and pericarditis, and the Fact Sheet for Recipients and Caregivers includes information about myocarditis and pericarditis.[109]

The Petition does not provide any new data or information regarding the risk of myocarditis. Petitioner's brief reference to this risk, which has been carefully considered by FDA when authorizing the Pfizer-BioNTech and Moderna COVID-19 Vaccines, does not alter FDA's conclusions with respect to the benefits and risks of these vaccines.

e. Petitioner's Statements Regarding Hospitalizations in the Moderna COVID-19 Vaccine Study

Petitioner asserts that "[t]he number of all-cause hospitalizations in the Moderna trial was higher in the vaccine group (17) than the placebo group (1)."[110] Petitioner further asserts that "FDA

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[107] Petition at 3. Petitioner also asserts that "Denmark, Finland, Norway, and Sweden suspended use of the Moderna vaccine for young populations last fall." While FDA communicates and works with international regulatory authorities on vaccine safety issues, regulatory authorities in other countries make decisions in the context of different laws and regulatory schemes, and do not dictate FDA's determinations about the benefits and risks of a particular product.

[108] See Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 4 Years of Age at 13-14, 60-63; Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 17 Years of Age at 13-14, 60-63.

[109] See, e.g., FDA, Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) Emergency Use Authorization (EUA) of the Moderna COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19), For 6 Months through 5 Years of Age (June 17, 2022), at 5, https://www.fda.gov/media/159307/download; For 6 Years through 11 Years of Age (June 17, 2022), at 6, https://www.fda.gov/media/159308/download; For 12 Years and Older (June 17, 2022), at 8, https://www.fda.gov/media/157233/download; FDA, Fact Sheet for Recipients and Caregivers Emergency Use Authorization (EUA) of the Moderna COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19), For 6 Months through 5 Years of Age (June 17, 2022), at 3, https://www.fda.gov/media/159309/download; For 6 Years through 11 Years of Age (June 17, 2022), at 3, https://www.fda.gov/media/159310/download; For 12 Years and Older (June 17, 2022), at 4-5, https://www.fda.gov/media/144638/download; FDA, Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19), For 6 Months through 4 Years of Age (June 17, 2022), at 10-11, https://www.fda.gov/media/159312/download; FDA, Fact Sheet for Recipients and Caregivers Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 (COVID-19), For 6 Months through 4 Years of Age (June 17, 2022), at 3, https://www.fda.gov/media/159313/download.

[110] Petition at 4.

counted only one of the 17 cases from the vaccine group, even though there were numerous febrile seizures and hospitalizations for other issues that could plausibly be linked to the shot."[111]

It appears that Petitioner may be referring to the number of Study P204 participants 6-23 months of age reporting serious adverse events (SAEs) not all of whom were reported as hospitalized.[112] In the open label and double blind parts of this study, SAEs were reported in 18 Moderna COVID-19 Vaccine recipients (3 and 15 recipients respectively) and 1 placebo recipient.[113] For one of these participants, a 1-year-old female, FDA considers the serious adverse events of a Grade 3 fever 6 hours after Dose 1 and a febrile convulsion 1 day after Dose 1 potentially related to the vaccine.[114] A febrile convulsion was reported in three other Moderna COVID-19 Vaccine recipients, these occurred: 21 days after dose 1, 10 days after dose 2, and 66 days after dose 2.[115] Each of these events was assessed as unrelated to the vaccine by FDA. Other unrelated SAEs reported in participants included, but are not limited to, mastoiditis, viral infection, diabetic ketoacidosis and foreign body in respiratory tract.[116] Although Petitioner asserts that certain of the SAEs assessed by FDA as unrelated to the vaccine "could plausibly be linked to the shot," Petitioner provides no new data or information regarding the events that would alter FDA's assessment.[117]

FDA considered the rates of adverse events and serious adverse events, in all age cohorts of the Moderna COVID-19 Vaccine studies (Studies P203 and P204), as part of FDA's assessment of the known and potential benefits and the known and potential risks of the Moderna COVID-19 Vaccine in individuals 6 months through 17 years of age. Petitioner does not provide any new data or information that would change FDA's evaluation of SAEs encountered during the Moderna COVID-19 Vaccine studies. For the reasons summarized in FDA's decision memorandum, FDA determined that the known and potential benefits of the Moderna COVID-19 Vaccine outweigh its known and potential risks, when used to prevent COVID-19 in individuals 6 months through 17 years of age.[118] Petitioner's above-referenced assertions relating to SAEs do not alter FDA's determination.

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[111] Id.
[112] Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 6 Months through 17 Years of Age, at 163-164.
[113] Id.
[114] Id.
[115] Id. at 165-67.
[116] Id.
[117] Petition at 4. Petitioner refers to the following document discussed earlier in this letter: Hollander, The "Safe and Effective" Moderna Covid Vaccine for Infants Might be Neither (June 29, 2022), https://doctorbuzz.substack.com/p/the-safe-and-effective-moderna-covid. As explained, this document appears to be an opinion piece that does not present any new data or information regarding the Moderna COVID-19 Vaccine that is of the scientific quality that FDA would consider in making regulatory decisions.
[118] For an extensive discussion of FDA's consideration of known and potential benefits and risks of the Moderna COVID-19 Vaccine see FDA's Moderna COVID-19 Vaccine EUA Decision Memorandum for Authorization in Individuals 6 Months through 17 Years of Age.

f. Petitioner's Claims Regarding Long-Term Immunity After Vaccination

Additionally, Petitioner claims that "recent research regarding Moderna's COVID vaccine suggests the injection may actually impair long-term immunity to the virus"[119] and urges FDA "to exercise extreme caution to avoid impairing the immune systems" of infants and children.[120] However, Petitioner's assertion that vaccination may hinder long-term immunity is not supported by the referenced study.[121] Accordingly, this does not change FDA's evaluation of the known and potential benefits and the known and potential risks of the Pfizer-BioNTech or Moderna COVID-19 Vaccine.

g. Petitioner's Claims Regarding Prior Infection

Petitioner also asserts there is "evidence that most, if not all, children have contracted COVID-19 already and thus have antibodies to the virus that are at least as effective as the COVID shots."[122] Petitioner provides no data or other information to support this claim. According to the CDC, "recovery from many viral infectious diseases is followed by a period of infection-induced immunologic protection against reinfection. This phenomenon is widely observed with many respiratory viral infections, including both influenza and the endemic coronaviruses, for which acquired immunity also wanes over time making individuals susceptible to reinfection." [123]

While there is scientific uncertainty about the duration of protection provided by natural infection with SARS-CoV-2, a recent study suggests that with increasing time since prior infection, vaccination provides greater protection against COVID-19 compared to prior infection alone.[124] There is also evidence that, among individuals previously infected with SARS-CoV-2, those who are unvaccinated are more likely to be reinfected compared with those who are fully vaccinated.[125]

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[119] Petition at 4.
[120] Id. at 5.
[121] Petition at 5. Petitioner cites to an article published by Israel National News (Rosenberg, D., COVID Vaccines May Impair Long-Term Immunity to the Virus, (May 24, 2022), https://www.israelnationalnews.com/news/328102) regarding research (Follmann, D., et al., Anti-Nucleocapsid Antibodies Following SARS-CoV-2 Infection in the Blinded Phase of the mRNA-1273 Covid-19 Vaccine Efficacy Clinical Trial, medRxiv (Apr. 19, 2022), preprint: 2022.04.18.22271936, doi: https://doi.org/10.1101/2022.04.18.22271936) that assessed the performance of immunoassays for determining past SARS-COV-2 infection in vaccinated individuals. This publication does not examine whether vaccine immunity is inferior to natural immunity or the duration of immunity following infection. We note that in the Preprint, the authors reported that "[anti-nucleocapsid antibodies] may have lower sensitivity in [Moderna COVID-19 Vaccine] vaccinated persons who become infected. Vaccination status should be considered when interpreting seroprevalence and seropositivity data based solely on antiN Ab testing."
[122] Petition at 5.
[123] CDC, Science Brief: SARS-CoV-2 Infection-induced and Vaccine-induced Immunity, last updated Oct. 2021, https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/vaccine-induced-immunity.html.
[124] See Nabin, et al., Necessity of Coronavirus Disease 2019 (COVID-19) Vaccination in Persons Who Have Already Had COVID-19, Clinical Infectious Diseases (Jan. 13, 2022), ciac022, https://doi.org/10.1093/cid/ciac022.
[125] CDC, Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination — Kentucky, May–June 2021, Morb Mortal Wkly Rep (Aug. 13, 2021), 70(32): 1081-1083, DOI: https://www.cdc.gov/mmwr/volumes/70/wr/mm7032e1.htm.

Petitioner has not shown that any periods of acquired immunity following natural infection serve to diminish the benefits of vaccination such that the known and potential benefits of the Pfizer-BioNTech and Moderna COVID-19 Vaccines do not outweigh the known and potential risks in the populations at issue in Petitioner's request.

h. Petitioner's Statements Regarding Biodistribution Studies

Petitioner states "[w]e know from the leaked Pfizer Biodistribution studies that the shot's Lipid Nanoparticles accumulate at high levels in the spleen, glands, and ovaries, yet the FDA has not studied or required the study of the injections' impact on reproductive health, even though independent research has already demonstrated concern on that topic with respect to the ovaries/menstruation in females and sperm in males."[126]

FDA addressed biodistribution studies in the June 2020 Guidance for Industry entitled "Development and Licensure of Vaccines to Prevent COVID-19," in which FDA recommended that "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."[127] 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."[128]

Regarding the effect of COVID-19 vaccines on reproductive health, studies suggest that COVID-19 vaccines do not reduce fertility[129], but may be linked to a small increase in menstrual cycle length.[130] Petitioner refers generally to "independent research" that "demonstrate[s] concern" on this topic; however, Petitioner does not cite to any such research or provide any other data relating to the effect of COVID-19 vaccines on reproductive health.

FDA finds no basis in Petitioner's assertions relating to biodistribution studies and reproductive health to change its conclusions with respect to the known and potential benefits and the known and potential risks of the Pfizer-BioNTech COVID-19 Vaccine in individuals 6 months through 4 years of age, or with respect to the known and potential benefits and the known and potential risks of the Moderna COVID-19 Vaccine in individuals 6 months through 17 years of age.

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[126] Petition at 4. Petitioner does not provide any citation to the "leaked studies" referenced.
[127] Vaccine Development and Licensure Guidance, at 7.
[128] Id.
[129] Wesselink, et al., A Prospective Cohort Study of COVID-19 Vaccination, SARS-CoV-2 Infection, and Fertility, Am J Epidemiol. (Jul. 23, 2022), 191(8): 1383-1395. doi: 10.1093/aje/kwac011.
[130] Edelman, et al., Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort, Obstet Gynecol (Apr. 1, 2022), 139(4): 481-489. doi: 10.1097/AOG.0000000000004695.

4. No Alternatives

For a product to be granted an EUA, section 564(c)(3) of the FD&C Act requires that "there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating [the serious or life-threatening disease or condition]." The Petition does not argue for revocation of the EUAs for the Pfizer-BioNTech and Moderna COVID-19 Vaccines for use in certain individuals on the grounds that there is an adequate, approved, and available alternative to prevent COVID-19, nor does it provide any information to support that such an alternative exists. Currently, the only FDA-approved drugs or biological products indicated to prevent COVID-19 in any population are Comirnaty and Spikevax. Comirnaty is approved for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older. Spikevax is approved for the prevention of COVID-19 in individuals 18 years of age or older.

Therefore, for the Pfizer-BioNTech COVID-19 Vaccine for children ages 6 months through 4 years of age, there are no adequate, approved and available alternatives, and the criterion under section 564(c)(3) of the FD&C Act is met.

Similarly, the criterion under section 564(c)(3) of the FD&C Act is met for the Moderna COVID-19 Vaccine for individuals ages 6 months through 17 years of age. Although Comirnaty is approved to prevent COVID-19 in certain individuals who fall within the scope of the Petition's request regarding FDA's authorization of the Moderna COVID-19 Vaccine (i.e., Comirnaty is approved in individuals 12 year of age and older, and the Petition requests that FDA revoke the EUA for the Moderna COVID-19 Vaccine for certain individuals, including for individuals 12 through 17 years of age), there is not sufficient approved vaccine available for distribution to this population in its entirety. Additionally, there are no COVID-19 vaccines that are approved to provide a COVID-19 vaccination in individuals younger than 12 years of age or a third primary series dose to certain immunocompromised populations described in the EUA for the Moderna COVID-19 Vaccine. Therefore, there are no adequate, approved, and available alternatives to the Moderna COVID-19 Vaccine for individuals 6 months through 17 years of age.

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

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

> significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data

> that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.[131]

As of the date of this writing, FDA has not identified any such circumstances that would make revocation of the Pfizer-BioNTech COVID-19 Vaccine EUA for use in individuals 6 months through 4 years of age or of the Moderna COVID-19 Vaccine EUA for use in individuals 6 months through 17 years of age appropriate to protect the public health or safety. As stated previously in this response, FDA determined the EUA standard is met for both the Pfizer-BioNTech and Moderna COVID-19 Vaccines in such individuals because data submitted by the sponsors demonstrated in a clear and compelling manner that the known and potential benefits of these vaccines, when used to prevent COVID-19, outweigh the known and potential risks, and that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating COVID-19 in these populations.

Additionally, as explained above, FDA finds no basis in the information submitted in the Petition, or in any post-authorization data regarding the Pfizer-BioNTech and Moderna COVID-19 Vaccines, to support a revocation of the Pfizer-BioNTech COVID-19 Vaccine EUA for use in individuals 6 months through 4 years of age or a revocation of the Moderna COVID-19 Vaccine EUA for use in individuals 6 months through 17 years of age. As described above, the Petition has not provided information demonstrating that that the known and potential benefits of the Pfizer-BioNTech and Moderna COVID-19 Vaccines in these populations are outweighed by the known and potential risks of these products.

Furthermore, there are no other circumstances that make a revision or revocation of the EUA for the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 6 months through 4 years of age or for the Moderna COVID-19 Vaccine for use in individuals 6 months through 17 years of age appropriate to protect the public health or safety, nor has Petitioner demonstrated that such circumstances exist. FDA therefore sees no justifiable basis upon which to take any action based on Petitioner's request regarding the Pfizer-BioNTech COVID-19 Vaccine EUA for use in individuals 6 months through 4 years of age and the Moderna COVID-19 Vaccine EUA for use in individuals 6 months through 17 years of age. Accordingly, as noted above, we deny Petitioner's request.

[131] EUA Guidance at 29.

IV. Conclusion

FDA has considered Petitioner's request to revoke the EUA for use of the Pfizer-BioNTech COVID-19 Vaccine in children ages 6 months through 4 years, and the EUA for use of the Moderna COVID-19 Vaccine in children ages 6 months through 17 years. For the reasons given above, FDA denies the Petition in its entirety.

Sincerely yours,

Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research

cc: Dockets Management Staff