June 17, 2022

Aaron Siri
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New York, NY 10166

Re: Citizen Petition (Docket Number FDA-2022-P-0872)

Sent via email to: [redacted]

Dear Mr. Siri,

This letter responds to the citizen petition dated May 20, 2022 that you submitted to the Food and Drug Administration (FDA, the Agency, we) on behalf of the Informed Consent Action Network (ICAN) (Petitioner) relating to: Emergency Use Authorizations (EUAs) for and development of vaccines to prevent Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (the Petition).

In the Petition, Petitioner requests that:

1. "the May 10, 2021 reissuance of the EUA for the use of Pfizer-BioNTech's COVID-19 vaccine for children ages 12 through 15 be revoked pursuant to 21 U.S.C. § 360bbb-3(g)";
2. "the FDA refrain from authorizing Moderna's current COVID-19 vaccine for children ages 12 through 17"; and
3. "the FDA require T-cell assessment from COVID-19 vaccine developers as a measure of evaluating vaccine efficacy."[1]

This letter responds to the Petition in full.[2] 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

[1] Petition at 3.

[2] The Petition states that it is submitted pursuant to 21 CFR 10.35, which applies to petitions for stay of action. Petition at 3. However, Petitioner's requests do not ask FDA to stay the effective date of any administrative action. Petitioner also describes the Petition as a "Citizen Petition" and follows the format prescribed in 21 CFR 10.30, rather than 10.35. See, e.g., Cover Letter accompanying Petition, available at, https://www.regulations.gov/document/FDA-2022-P-0872-0001. We therefore construe the Petition as one submitted under 21 CFR 10.30. Assuming, arguendo, that the Petition could constitute a proper request for a stay of action, we address in section III.D why a stay is not justified.

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

Here is an outline of our response:

I. BACKGROUND

There is currently a pandemic of respiratory disease, COVID-19, caused by a novel coronavirus, SARS-CoV-2. The COVID-19 pandemic presents an extraordinary challenge to global health. On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19.[3] 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

[3] 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.

or the health and security of United States (U.S.) citizens living abroad, and that involves the virus that causes COVID-19.[4] 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.[5] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[6]

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 February 27, 2021, FDA issued EUAs for three vaccines to prevent COVID-19, including vaccines sponsored by Pfizer Inc. (Pfizer),[7] ModernaTX, Inc. (Moderna)[8] and Janssen BioTech, Inc. (Janssen) (the "Authorized COVID-19 Vaccines"). The EUAs have been amended since initial issuance.

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 16 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 Moderna. 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

[4] 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.
[5] 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.
[6] 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/.
[7] Hereinafter "Pfizer-BioNTech COVID-19 Vaccine".
[8] Hereinafter "Moderna COVID-19 Vaccine"
[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).

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 of drugs are set out at 21 CFR Part 312.

Before conducting a clinical investigation in the U.S. in which a new drug or biological product is administered to humans, a sponsor must submit an investigational new drug application (IND) to FDA.[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

[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.

[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 participants 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).

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, in some cases, be in the thousands or tens of thousands of subjects. Phase 3 studies provide the critical documentation of effectiveness and important additional safety data required for licensing.

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

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[17] Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products, 78 FR 12937, 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).

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 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 that can be caused by a chemical, biological, radiological, or nuclear agent or agents identified in an EUA declaration made by the Secretary 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]

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[23] FDA, Vaccines, last updated January 2021, 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 this declaration and determination, under section 564(c) of the FD&C Act, FDA may issue an EUA during the COVID-19 pandemic after FDA concludes that the following statutory requirements are met:

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

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

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

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

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

In a Phase 3 study of a COVID-19 vaccine, the efficacy of the investigational vaccine to prevent disease will be assessed by comparing the number of cases of disease in each study group. For

[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.

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-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]

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

III. DISCUSSION

A. Petitioner's Request that FDA Revoke the May 10, 2021 Emergency Use Authorization for the Use of the Pfizer-BioNTech COVID-19 Vaccine in Individuals Ages 12 through 15

In this section, we address Petitioner's request that "the May 10, 2021 reissuance of the EUA letter of authorization for the use of [the Pfizer-BioNTech] COVID-19 vaccine for children ages 12 through 15 be revoked pursuant to 21 U.S.C. § 360bbb-3(g)[.]"[33, 34]

i. EUA for 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, 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.[35] Currently, the Pfizer-BioNTech COVID-19 Vaccine[36] is authorized for emergency use as a:

- 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 5 months after completing a primary series of the Pfizer-BioNTech COVID-19 Vaccine or Comirnaty
- 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

[33] Petition at 3.
[34] We note that the Petition discusses several assertions made or actions taken by CDC. For requests intended for CDC, you should contact CDC directly.
[35] For a description of all revisions to the EUA for Pfizer-BioNTech COVID-19 vaccine, see Pfizer-BioNTech COVID-19 Vaccine Letter of Authorization, June 17, 2022. This Letter of Authorization will be posted on www fda.gov.
[36] 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.

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 4 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 4 months after receipt of a first booster dose of any authorized or approved COVID-19 vaccine
- Three-dose primary series for individuals 6 months through 4 years of age.

Petitioner specifically requests that FDA revoke the "May 10, 2021 reissuance of the EUA letter of authorization for the use of [the Pfizer-BioNTech] COVID-19 vaccine for children ages 12 through 15[.]"[37] However, as noted above, subsequent to May 10, 2021, FDA reissued the letter of authorization for emergency use of the Pfizer-BioNTech COVID-19 Vaccine to incorporate other revisions related to individuals 12 through 15 years of age. We therefore interpret the Petition to request revocation of the EUA for the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 12 through 15 years of age.

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 incorporates by reference the EUA Review Memoranda for the Pfizer-BioNTech COVID-19 Vaccine,[38] which discuss this determination, and the data upon which it was based, in detail.[39]

ii. The Standard for Revocation of EUAs Is Not Met

Petitioner argues that the May 10, 2021 authorization of the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 12-15 years of age "was unlawful at the time it was issued" and should be revoked because (1) there was and continues to be "no emergency" in this age group, (2) "[t]he clinical trial relied upon to authorize Pfizer's vaccine in 12- to 15-year-olds was deficient," (3) "[t]he alleged benefits of Pfizer's vaccine for 12- to 15-year-olds are heavily outweighed by the known and potential risks."[40] Petitioner has provided no basis to demonstrate that the EUA should be revoked. In this section, we address Petitioner's specific arguments.

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[37] Petition at 3.

[38] 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.

[39] 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.

[40] Petition at 4-5, 9-10.

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, FDA "*may* revise or revoke" an EUA.[41] The verb "may" is ordinarily permissive, particularly when the statute elsewhere uses the term "shall" to confer a mandatory duty.[42] Further underscoring FDA's discretion, the EUA statute explicitly provides that all decisions regarding EUAs are "committed to agency discretion."[43]

A permissive reading of "may" also accords with the statutory purpose of giving FDA flexibility to "permit rapid distribution of promising new drugs and antidotes in the most urgent circumstances,"[44] 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])."[45] 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.

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[41] Section 564(g)(2) of the FD&C Act (emphasis added).
[42] See *Old Line Life Ins. Co. of Am. v. Garcia*, 411 F.3d 605, 614-615 (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."
[43] 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].").
[44] *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).
[45] EUA Guidance at 28.

iii. Circumstances Described under Section 564(b)(1) of the FD&C Act 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.[46] 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)).[47]

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 that the circumstances described under section 564(b)(1) no longer exist.[48] You therefore have not shown that there are grounds for revoking the authorization of the Pfizer-BioNTech COVID-19 Vaccine for 12-15-year-olds 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).

iv. 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

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[46] 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.

[47] COVID-19 EUA Declaration.

[48] Petitioner states that "[t]o invoke Section 564, there must be an emergency necessitating an action under the statute. Specifically, COVID-19 would have to cause [a] serious or life-threatening disease or condition for 12- to 15-year-olds in order to justify an EUA." Petition at 4. We interpret Petitioner's assertion that there is "no health emergency" for children to be an argument regarding the criterion for issuing an EUA under section 564(c)(1) of the FD&C Act. To the extent the Petitioner's assertion is intended to address the determination under section 564(b)(1)(C) of the FD&C Act, that provision does not contemplate separate public health emergency determinations by age group. Rather, it provides that FDA may not issue an EUA unless the Secretary determines "that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves a biological, chemical, radiological, or nuclear agent or agents, or a disease or condition that may be attributable to such agent or agents." Thus, the Petition makes no showing that this statutory standard is not met.

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 12-15 years of age and why, therefore, FDA is not revoking the EUAs for the Pfizer-BioNTech COVID-19 Vaccine for use in that population 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 June 11, 2022, has caused more than 500 million cases of COVID-19 and claimed the lives of more than 6 million people worldwide.[49] In the United States, as of June 11, 2022, more than 85 million cases and over 1 million deaths have been reported to the Centers for Disease Control and Prevention (CDC).[50] On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS, and the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Additional background information on the SARS-CoV-2 virus and COVID-19 pandemic may be found in FDA's decision memoranda regarding the Pfizer-BioNTech COVID-19 Vaccine EUA.[51]

Petitioner argues that there was—when FDA first authorized emergency use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age—and continues to be "no emergency in this age group[,]" claiming that there is "not a severe or deadly pandemic for children."[52] The Petition states that, "[s]pecifically, COVID-19 would have to cause [a] serious or life-threatening disease or condition for 12- to 15-year-olds in order to justify an EUA."[53] To the extent this constitutes an argument that SARS-CoV-2 cannot cause a serious or life threatening disease or condition in this population, FDA disagrees.

With respect to the impact of the SARS-CoV-2 pandemic on individuals within the age groups at issue in Petitioner's requests, as of June 11, 2022, approximately 5.7 million COVID-19 cases in individuals 12-17 years of age have been reported to the CDC.[54] Some of these cases have resulted in hospitalization and death. The cumulative rate of COVID-19 associated hospitalization was 125.1 per 100,000 for the 12-17 years of age population as of June 4, 2022

[49] Johns Hopkins University School of Medicine, Coronavirus Resource Center, https://coronavirus.jhu.edu/map.html (accessed June 11, 2022).
[50] CDC, COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#datatracker-home (accessed June 11, 2022).
[51] See FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda.
[52] Petition at 4-5, 9-10.
[53] Petition at 4. 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 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 12-15 years of age.
[54] CDC, Demographic Trends of COVID-19 cases and deaths in the US reported to CDC, https://covid.cdc.gov/covid-data-tracker/#demographics (accessed June 11, 2022).

based on COVID-NET data reported to the CDC.[55, 56] As of June 12, 2022, 382 deaths associated with COVID-19 have been reported among individuals ages 12 through 15, and 310 deaths reported among individuals 16 through 17.[57] 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.[58]

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 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 May 31, 2022, the CDC received reports of 8,525 cases and 69 deaths that met the definition for MIS-C.[59]

By its own terms, the Petition appears to acknowledge that the SARS-CoV-2 virus can cause a serious or life-threatening disease or condition. For example, Petitioner asserts that "only a subset of identifiable children with underlying conditions are potentially at risk for serious or

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[55] CDC, COVID-NET Laboratory-confirmed COVID-19 hospitalizations, https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network (accessed June 12, 2022). The current network covers nearly 100 counties.

[56] Although the Petition cites CDC data as evidence of "low numbers related to pediatric hospitalizations and deaths" from COVID-19, Petitioner simultaneously makes several assertions suggesting that CDC data have been "inflated." Petition at 5, 9-10. For example, the Petition cites a CDC report based on COVID-NET data regarding hospitalization of adolescents to support the proposition that there has "been an apparent continued effort to inflate COVID-19 numbers in children and induce fear among parents[.]" Petition at 5. While questions or requests about CDC data should be directed to CDC, we note that 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 May 11, 2022); CDC, About CDC COVID-19 Data, https://www.cdc.gov/coronavirus/2019-ncov/covid-data/about-us-cases-deaths.html (last updated Sept. 7, 2021). The Petition provides no new information about the limitations of CDC COVID-19 data sources; it also provides no evidence showing that there has been an effort to "induce fear among parents."

[57] CDC, Demographic Trends of COVID-19 cases and deaths in the US reported to CDC, https://covid.cdc.gov/covid-data-tracker/#demographics (accessed June 12, 2022).

[58] 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: 489–494, 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.").

[59] 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 June 4, 2022).

life-threatening disease."[60] Petitioner cites only one article published in the *Journal of Infection* in support of the statement that "myriad studies have shown that COVID-19 is not a serious threat even to immunocompromised children."[61] However, the authors do not conclude that severe COVID-19 or death cannot occur in immunocompromised children; the article summary states that the "study shows SARS-CoV-2 infections have occurred in immunocompromised children and young people with no increased risk of severe disease" and reports that no children participating in the study died.[62] The article further acknowledges that "[a] large systematic review with meta-analysis and a large retrospective cross sectional study, found paediatric (sic) patients with chronic health conditions were at higher risk of severe COVID-19 compared to those without."[63] Finally, the authors note that the study occurred before the Delta variant became the predominant strain, and that this "emphasi[z]es the need for ongoing surveillance of the impact of variant strains on the risk to immunocompromised children."[64]

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 12-15 years of age, nor has Petitioner demonstrated that to be the case. The Petition thus fails to establish that the criterion under section 564(c)(1) is no longer met for the Pfizer-BioNTech COVID-19 for use in this population.

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 in preventing, diagnosing, or treating the identified serious or life-threatening disease or condition that can be caused by the agent identified in the EUA declaration (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

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[60] Petition at 4. The Petition also cites several publications and the CDC website to support the assertion that deaths from COVID-19 were rare among children and that hospitalization rates of children with COVID-19 are low, rather than for the proposition that death or severe COVID-19 does not occur as a result of infection with the SARS-CoV-2 virus. See Petition at 4-5 nn. 4-7, 9-12; Petition at 9 nn. 35-37. Therefore, the citations do not alter our analysis, and this response does not address them in detail, although we do not necessarily agree with Petitioner's characterization of all these sources. For example, Petitioner cites a CDC report that found "eight in-hospital COVID-19-related deaths in persons aged 0-17 occurred during August 2020-August 2021" as evidence that there is absence of risk to adolescents. Petition at 9 n.36 (citing Siegel, et. al, Trends in COVID-19 Cases, Emergency Department Visits, and Hospital Admissions Among Children and Adolescents Aged 0–17 Years — United States, August 2020–August 2021, Morb Mort Wkly Rep., at 3 (Sept. 3, 2021), 70, https://stacks.cdc.gov/view/cdc/109525). Petitioner does not mention the same article's findings that 1,790 COVID-19 hospitalizations occurred among persons aged 0-17 years during that same period and that "[d]uring a 2-week period in August 2021, COVID-19–associated ED visits and hospital admissions for children and adolescents with confirmed COVID-19 were highest in states with lowest vaccination coverage, particularly states in the South, whereas in the states with the highest coverage, COVID-19 ED visits and the rate of hospital admissions among children and adolescents were lowest." Id. at 2-3.

[61] Petition at 4.

[62] Chappell, et al., Immunocompromised children and young people are at no increased risk of severe COVID-19, Journal of Infection (Jan. 2022), 84(1): 31-39, https://doi.org/10.1016/j.jinf.2021.11.005.

[63] Id. at 32.

[64] Id. at 37.

believe that the Pfizer-BioNTech COVID-19 Vaccine may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition in the 12-15 years of age population. The basis for this determination is explained in detail in FDA's decision memoranda regarding the Pfizer-BioNTech COVID-19 Vaccine EUA.[65]

Petitioner raises concerns about the adequacy of clinical data relied upon to authorize the Pfizer-BioNTech COVID-19 Vaccine for emergency use in individuals 12-15 years of age.[66] 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.

Petitioner argues that "the clinical trial relied upon to authorize Pfizer's vaccine in 12- to 15-year-olds was inadequate to properly test efficacy[.]"[67] On May 10, 2021, FDA authorized the emergency use of Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 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 2,260 participants 12-15 years of age (Study C4591001).[68] We therefore interpret Petitioner's arguments to be in reference to this study.

According to Petitioner, Study C4591001 was inadequate because it "was limited to assessing antibody levels and comparing those levels to adult levels using immunobridging."[69] Petitioner asserts that using immunobridging to assess vaccine effectiveness is flawed because "it assumes GMT titers generated against the outdated parental spike protein are sufficient to neutralize current and future SARS-CoV-2 spike protein variants in a different, younger, cohort" and because the correlation between antibody levels and protection from COVID-19 is currently unknown.[70]

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.[71] In addition, a study may not be needed in each pediatric age

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

[66] See Petition at 5-6, 10-13.

[67] Petition at 5. We note that the Petition also argues that the clinical trial was inadequate to properly assess safety and to justify FDA's benefit-risk assessment. We address those arguments below in section III.A.iv.3 regarding the criterion in section 564(c)(2)(B) of the FD&C Act (i.e., 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).

[68] See FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), at 5, https://www fda.gov/media/148542/download.

[69] Petition at 7. The Petition also asserts that immunobridging was used "because COVID rarely causes disease in children and hence not enough children would likely become infected during the trial to assess the real-life efficacy." Petition at 7. To the extent that this is to dispute that there is a serious or life-threatening disease or condition, we address that issue above.

[70] Petition at 7.

[71] 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").

group if data from one age group can be extrapolated to another age group.[72] 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.

To the extent Petitioner argues that there was insufficient evidence to determine that Pfizer-BioNTech COVID-19 Vaccine may be effective to prevent COVID-19 in individuals in 12-15 years of age because its authorization for such use was based, in part, on immunobridging data, we disagree. 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 a young 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.[73]

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 Petitioner notes, and FDA acknowledged at the time of its May 10, 2021 decision, no specific neutralizing antibody titer has been established to predict protection against COVID-19.[74] Because of this, we consider 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. Thus, to the extent that the Petition asserts that the effectiveness criterion for issuance of EUAs was not or is no longer met on the basis of the choice of endpoints for Study C4591001, we disagree. The Petition has not shown that the choice of endpoints is inappropriate, or that the study failed to provide evidence that the vaccine may be effective. The Petition thus fails to establish that the criterion under section 564(c)(2)(A) is no longer met for the Pfizer-BioNTech COVID-19 for use in this population.

3. Benefit-Risk Analysis

Section 564(c)(2)(B) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "the known and potential benefits of the product, when used to diagnose, prevent, or treat [the identified serious or life-threatening disease or condition], outweigh the known and potential risks of the product . . . ." FDA authorized the Pfizer-BioNTech COVID-19 Vaccine for emergency use in individuals 12-15 years of age after reaching a determination that, among other things, the known and potential benefits of the

[72] 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").
[73] 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 12-15 Years of Age (May 10, 2021) at 5 https://www.fda.gov/media/148542/download.
[74] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021) at 10, https://www.fda.gov/media/148542/download.

vaccine, when used to prevent COVID-19 in this population, outweigh its known and potential risks.[75]

Petitioner raises concerns about the adequacy of "the clinical trial relied upon to authorize the [Pfizer-BioNTech COVID-19 Vaccine] in 12- to 15- year-olds"[76] to properly assess safety and support a benefit-risk assessment.[77] In addition, Petitioner notes post-authorization concerns related to rates of infection in vaccinated individuals, effectiveness against emerging variants, "the current rate of natural immunity," and numerous concerns regarding safety of the Pfizer-BioNTech COVID-19 Vaccine.[78] Due to these concerns, Petitioner argues that the EUA for the Pfizer-BioNTech COVID-19 Vaccine should be revoked with respect to individuals 12-15 years of age because "[t]he alleged benefits of Pfizer's vaccine for 12- to 15-year-olds are heavily outweighed by the known and potential risks."[79] 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)(B) is satisfied.

a. Petitioner's Claims Regarding Adequacy of Clinical Trial Safety Data

Petitioner makes several arguments regarding the adequacy of Study C4591001 to support FDA's benefit-risk assessment when it originally authorized use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age on May 10, 2021.[80] For the reasons explained above in section III.A.iv.2, Petitioner has not provided information establishing that this Study was inadequate to assess effectiveness. In this section, we address Petitioner's additional arguments related to the adequacy of Study C4591001 to assess safety.

Trial Size and Duration

The Petition asserts that because Study C4591001 "included only 2,260 participants, half of whom received the vaccine and half of whom received a placebo," the number of participants in Study C4591001 was inadequate to detect any potential adverse event "should the rate of injuries be above one in 2,500."[81] In addition, Petitioner argues that Study C4591001 was of insufficient duration because it only collected safety data for "a few months."[82]

As a general matter, FDA evaluates study design of a clinical trial during the normal course of review of an IND, an EUA request, or a BLA application. This review includes an evaluation of study plans and protocols regarding documentation and evaluation of adverse events. FDA

[75] For an extensive discussion of FDA's analysis of the clinical trial data regarding the risks and benefits of the Pfizer-BioNTech COVID-19 Vaccine, see FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda.
[76] As explained above, we interpret this as a reference to data provided in support of the EUA amendment request from Study C4591001 for participants 12-15 years of age.
[77] Petition at 5.
[78] Id. at 10-18.
[79] Id. at 10.
[80] Id. at 5-6, 8.
[81] Id. at 5-6.
[82] Id. at 8.

evaluated study plans and protocols for Study C4591001 to help ensure that they were appropriate and adequate to ensure that the risks to participants are minimized and that the study could support authorization or licensure.

A decision about the appropriate length of safety studies is based on various factors, including the intended use of the product, the nature of the labeled patient population, and earlier clinical and preclinical safety assessments.[83] FDA's EUA Vaccine Guidance recommends that, to support an EUA for a COVID-19 vaccine, data from Phase 3 studies (which may result from a protocol-specified interim analysis) include a median follow-up duration of at least 2 months after completion of the full vaccination regimen.[84] This guidance reflects the Agency's assessment that, from a safety perspective, a 2-month median follow-up after completion of the full vaccination regimen (meaning that at least half of vaccine recipients in clinical trials have at least 2 months of follow-up) will allow identification of potential adverse events that were not apparent in the immediate post-vaccination period.[85] Adverse events considered plausibly linked to vaccination generally start within 6 weeks after vaccine receipt.[86] Two months of follow-up should, therefore, provide time for detection of adverse events that began within this 6-week period to be observed and evaluated.

For purposes of the EUA amendment request, FDA's review focused on safety data from Study C4591001 for participants 12-15 years of age and a comparison group of participants 16-25 years of age.[87] As of the data cutoff, a total of 2,260 adolescents 12-15 years of age (1,131 in the vaccinated group and 1,129 in the placebo group) were enrolled and contributed to the safety population, with a median of greater than 2 months of follow-up after the second dose. For the safety comparator group, a total of 3,770 participants 16-25 years of age (1,867 in the vaccinated group and 1,903 in the placebo group) were enrolled and contributed to the safety population.[88] Considering the burden of COVID-19 in the adolescent age group, the follow-up period was justified based on the need for a vaccine to address the pandemic and the demonstration of vaccine effectiveness to support the favorable benefit-risk profile for the use of the vaccine in this population under an EUA.

To support its arguments regarding the inadequate power, size, and duration of the study, Petitioner points to CDC's Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) review of the Pfizer-BioNTech COVID-19 Vaccine for individuals 12-15 years of age, which was presented to the Advisory Committee for Immunization Practices (ACIP) on May 12, 2021 ("GRADE Review").[89] Petitioner states that the GRADE Review

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[83] Premarketing Risk Assessment; Guidance for Industry, March 2005 at 9; https://www.fda.gov/media/71650/download.
[84] EUA Vaccine Guidance at 10-11.
[85] FDA, Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020 FDA Briefing Document at 10, available at https://www.fda.gov/media/144245/download.
[86] Health Resources and Services Administration, Vaccine Injury Table, 2022, https://www.hrsa.gov/sites/default/files/hrsa/vicp/vaccine-injury-table-01-03-2022.pdf.
[87] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), at 10, https://www fda.gov/media/148542/download.
[88] Id. at 6, 12-13.
[89] Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Pfizer-BioNTech COVID-19 Vaccine for Persons Aged 12-15 Years, Presented to ACIP on May 12, 2021, https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-pfizer-biontech-vaccine-12-15-years.html.

noted concerns that the body of evidence for use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age did "not provide certainty that rare serious adverse events were captured due to the short follow-up and sample size" and due to the width of the confidence interval.[90] While the GRADE Review indicates the certainty in estimates from the available body of evidence— ranging from type 1 (high certainty) to type 4 (very low certainty)—the review does not address whether the totality of the scientific evidence available at the time of the review indicated that the known and potential benefits of the vaccine outweighed its known and potential risks for use in individuals 12-15 years of age, and we note that ACIP ultimately voted to recommend the "Pfizer-BioNTech COVID-19 [V]accine . . . for persons 12-15 years of age in the US population . . . under an Emergency Use Authorization."[91]

We also note that FDA's review of the EUA amendment request for use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age took into account the safety data provided on individuals 16 years of age and older and post-authorization data on individuals 16 years of age and older.[92] In addition, when FDA originally authorized the Pfizer-BioNTech COVID-19 Vaccine for use in this population, FDA specifically recognized that "use in large numbers of individuals 12-15 years of age may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population" and that [a]ctive and passive safety surveillance [would] continue during the post authorization period to detect new safety signals."[93] As explained below, FDA has reviewed post-authorization data and taken action to address new safety signals that arose. In reviewing the EUA amendment request, FDA found that Study C4591001 was of sufficient size and duration 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 12-15 years of age. Petitioner has provided no information regarding the duration or size of Study C4591001 that alters this determination.

Thus, to the extent that the Petition asserts that the risk-benefit criterion for issuance of EUAs is no longer met on the basis of a clinical trial that was too small or of insufficient duration, we disagree. The Petition has not shown that the trial was too small or had an insufficient follow-up period 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 12-15 years of age.

Trial Population

Petitioner also argues that Study C4591001 is "problematic" because it "was not representative of most American children" in that it "only included 'healthy participants' and excluded those

[90] Petition at 6.
[91] See Meeting Of The Advisory Committee On Immunization Practices (ACIP) Summary Minutes (May 12, 2021), at 9-12, 31, https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/summary-2021-05-12-508.pdf.
[92] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), at 24-35, https://www fda.gov/media/148542/download.
[93] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), at 39, https://www fda.gov/media/148542/download.

who were previously infected with SARS-CoV-2."[94] Petitioner claims that this resulted in excluding a large proportion of the population because "at least 37% of children were estimated by the CDC to have been infected with SARS-CoV-2 as of May 2021 and 43% are estimated to have [a] chronic health condition."[95] The Petition further notes that "the 12- to 15-year-olds in the trial were approximately 86% White and only 12% Hispanic or Latino, and only 567 boys were vaccinated in the trial."[96]

FDA recognizes that the risks of SARS-CoV-2 infection can differ across population groups. In the Vaccine Development and Licensure Guidance, FDA noted that while certain exclusions were recommended, for example "[e]xclusion of participants at higher risk of severe COVID-19 from early phase studies" in order "to mitigate potential risk of vaccine associated [enhanced respiratory disease] until additional data to inform that potential risk becomes available through ongoing product development," FDA in general "encourages inclusion of diverse populations in all phases of vaccine clinical development."[97] FDA also noted that "vaccine safety and COVID-19 outcomes in individuals with prior SARS-CoV-2 infection, which might have been asymptomatic, is also important to examine because pre-vaccination screening for prior infection is unlikely to occur in practice with the deployment of licensed COVID-19 vaccines."[98] Although the Vaccine Development and Licensure Guidance includes various recommendations, ultimately FDA's decisions on an EUA or EUA amendment request are based on the totality of the available scientific evidence.

Petitioner incorrectly asserts that Study C4591001 "only included 'healthy participants and excluded those who were previously infected with SARS-CoV-2 infection."[99] Petitioner also states that "only 567 boys were vaccinated in the trial"[100]; but it is unclear how this relates to males being under-represented in the study population of participants 12-15 years of age. There were 567 males identified in the vaccinated group (50.1%); there were also 585 males in the placebo group (51.8%).[101] Thus, in both the vaccinated and control groups, males were approximately 50% of the 12-15 year-old trial population. Petitioner has provided no scientific justification or information showing that the clinical data submitted to FDA were insufficiently representative to support authorization of the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 12-15 years of age. Thus, Petitioner's argument regarding the representativeness of the trial population does not alter FDA's determination that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks for individuals 12-15 years of age.

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[94] Petition at 6.
[95] Id.
[96] Id.
[97] Vaccine Development and Licensure Guidance at 10-11.
[98] Id. at 11.
[99] See FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), at 16-18 https://www fda.gov/media/148542/download (summarizing demographics and other baseline characteristics of participants 12-15 years of age in the dose 2 evaluable immunogenicity population and in the safety population, including with respect to comorbidities and baseline evidence of prior SARS-CoV-2 infection); see also id. at 5, 22.
[100] Petition at 6.
[101] Perez, J., Pfizer, COVID-19 Vaccine BNT162b Safety, Immunogenicity, and Efficacy in Subjects 12-15 years-old: Presentation to ACIP, at 4 (May 21, 2021), https://www.cdc.gov/vaccines/acip/meetings/slides-2021-05-12.html.

Adverse Events

Petitioner also contends that "[e]ven the adverse events that were picked up by the clinical trial pointed to serious issues from the start."[102] Petitioner further asserts that "the study itself refuted the idea that vaccinating this age group would provide any real benefit" because no participants got severe COVID-19, were hospitalized for COVID-19, or died from it and "therefore any adverse event, of which there were several, is of great consequence." [103] Petitioner has provided no new information to the Agency or a scientific justification in support of these arguments.

During its review of the EUA amendment request to authorize the use of Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age, FDA determined that reported serious adverse events among participants, while uncommon, "represented medical events expected to occur among individuals in this age group and with the underlying conditions represented in the study population" and that "available data [did] not suggest a causal relationship to [the vaccine]."[104] As part of its review, FDA also considered longer-term safety data from participants 16 years of age and older, as well as safety surveillance data from use of the vaccine under EUA. FDA review of these data did not raise safety concerns,[105] other than "a documented incidence of anaphylaxis (occurring primarily among individuals with history of severe allergic reaction to other medications or foods) of 0.46 cases per million doses administered, similar to reported rates of anaphylaxis following licensed preventive vaccines."[106] In addition, as a result of post-authorization safety monitoring, FDA subsequently became aware of increased risks of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the tissue surrounding the heart) following vaccination that justified revising the patient and provider fact sheets for the Pfizer-BioNTech COVID-19 vaccine regarding the

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[102] Petition at 8. In support of this contention, Petitioner cites CDC's GRADE for Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age, noting that "10.7% of participants reported Grade 3 or higher adverse events within the trial." Id. According to CDC's GRADE Review, 10.7% of vaccine recipients in the study reported reactogenicity, which includes local and systemic events Grade ≥ 3; a Grade 3 event "prevents daily routine activity or requires use of a pain reliever" and a Grade 4 event "requires emergency room visit or hospitalization." The CDC's GRADE Review indicated that there was one participant in the vaccine group that reported a Grade 4 event. See Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Pfizer-BioNTech COVID-19 Vaccine for Persons Aged 12-15 Years, Presented to ACIP on May 12, 2021, https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-pfizer-biontech-vaccine-12-15-years.html.

[103] Petition at 8.

[104] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), at 6, https://www fda.gov/media/148542/download.

[105] We note that the Petition indicates that one of the trial participants suffered serious adverse events immediately after receiving a second dose of the Pfizer-BioNTech COVID-19 Vaccine. Petition at 6. Petitioner states that "[d]espite the clear medical records and documentation of her immediate and serious injuries," this "life-altering reaction was classified as mere 'functional abdominal pain'" in the data Pfizer submitted to FDA to support its EUA amendment request. Id. Petitioner argues that this shows "the risk of adverse events from this vaccine in this population is so great that even an underpowered clinical trial identified a devastating and life altering serious adverse event, even if Pfizer didn't acknowledge it as such." Id. FDA takes all reports of adverse events potentially related to vaccines seriously. To the extent that the Petition is asserting that Pfizer provided inaccurate information in its EUA submission to FDA, resolving any such allegation is outside the scope of your requested actions in this citizen petition. To the extent that the Petition is suggesting that there is a high rate of serious adverse events that undermines FDA's benefit-risk conclusions, the Petition does not provide evidence of such.

[106] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), at 6, https://www fda.gov/media/148542/download.

suggested increased risk.[107] The Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was revised to include a warning about myocarditis and pericarditis and the Fact Sheet for Recipients and Caregivers was revised to include information about myocarditis and pericarditis. The warning in the current Fact Sheets for Healthcare Providers Administering Vaccines state that post-marketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose.[108] Additionally, the Fact Sheets for Recipients and Caregivers for this vaccine note that vaccine recipients should seek medical attention right away if they have chest pain, shortness of breath, or feelings of having a fast-beating, fluttering, or pounding heart after vaccination. The FDA and CDC are monitoring the reports, collecting more information, and conducting activities to assess longer-term outcomes. Despite this risk, FDA continues to conclude that the known and potential benefits of the vaccine outweigh the known and potential risks. [109]

Further, FDA disagrees with Petitioner's assertion that the clinical data provided in support of the EUA amendment request "refuted the idea that vaccinating this age group would provide any real benefit." These data included a demonstration of effectiveness through immunobridging, as well as a supplemental efficacy analysis, which demonstrated the benefit of reduction in the risk of confirmed COVID-19, relative to placebo as described in FDA's May 10, 2021 decision memorandum. Although there were no cases of severe COVID-19 or COVID-19-related death reported among study participants, for the reasons described above in section III.A.iv.1, COVID-19 can be serious or life-threatening for individuals in this age group.

For the reasons summarized in FDA's May 10, 2021 decision memorandum, FDA determined that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweighed its known and potential risks. Petitioner has not supported its arguments that Study C4591001 raised "serious safety issues" or that the study demonstrated the Pfizer-BioNTech COVID-19 Vaccine would not provide "any real benefit" in 12-15 year-olds. Therefore, those arguments do not alter FDA's determination.

b. Petitioner's Claims Regarding Breakthrough Infections

Petitioner notes that after FDA authorized the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 12-15 years of age, "it became apparent that children receiving the [Pfizer-BioNTech COVID-19 Vaccine] can still become infected with and transmit the virus."[110] Petitioner suggests that this raises concerns regarding post-authorization effectiveness and argues that the EUA should thus be revoked because the current risks of the vaccine outweigh its benefits for

[107] FDA, Coronavirus (COVID-19) Update: June 25, 2021, https://www fda.gov/news-events/press-announcements/coronavirus-covid-19-update-june-25-2021.

[108] Fact Sheet for Healthcare Providers Administering Vaccine, Revised June 1, 2022 (For 12 years of age and older, dilute before use), https://www.fda.gov/media/153713/download; Fact Sheet for Healthcare Providers Administering Vaccine, Revised May 17, 2022 (For 12 years of age and older, do not dilute), https://www.fda.gov/media/153715/download.

[109] We note that this is consistent with the conclusions reached by ACIP, which reviewed an individual-level assessment that compared the benefits (i.e., COVID-19 infections and severe disease prevented) to the risks (number of cases of myocarditis) of vaccination. See CDC, Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, Morb Mortal Wkly Rep. (June 2021), 70: 977–982, DOI: http://dx.doi.org/10.15585/mmwr.mm7027e2external icon.

[110] Petition at 10.

individuals 12-15 years of age.[111] In support of this argument, Petitioner cites several publications and claims that they "found the same rate of infection among the vaccinated and unvaccinated, with each having the same viral load in their nasal cavity."[112] However, this argument fails to show that the criterion for issuance of the EUA (i.e., that the known and potential benefits outweigh the known and potential risks) is no longer met.

While there is evidence that the circulating variants of concern may infect vaccinated individuals, it is important to note that the Pfizer-BioNTech COVID-19 Vaccine is authorized to prevent COVID-19 in individuals 12-15 years of age, not to prevent SARS-CoV-2 infection or transmission.[113] Furthermore, post-authorization data regarding the Pfizer-BioNTech COVID-19 Vaccine continues to support that the vaccine prevents severe consequences of COVID-19.[114] Finally, a vaccine does not need to be 100% effective in preventing the target disease to meet the licensure or EUA standard. It is expected that some vaccinated individuals will contract the target disease despite having been vaccinated against it.

No FDA licensed or authorized vaccine is 100% effective, but scientific data have nevertheless demonstrated that vaccinations have been a very effective approach to protecting the public's health in the United States.[115] Similarly, a COVID-19 vaccine need not be 100% effective in preventing COVID-19, or even close to 100% effective in doing so, in order to have a significant effect in altering the course of the COVID-19 pandemic and for the known and potential benefits to outweigh the known and potential risks.

As explained above, the Pfizer-BioNTech COVID-19 Vaccine is authorized to prevent COVID-19, not to prevent SARS-CoV-2 infection or transmission. Regardless, the publications cited by Petitioner to support that the "rate of infection is the same among the vaccinated and unvaccinated" do not, in fact, show this to be the case. These publications include reports of public health investigations of outbreaks of COVID-19 cases that identify COVID-19 cases among both vaccinated and unvaccinated individuals.[116] They also include a study to determine

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[111] Id.
[112] Id.
[113] See, e.g., FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Letter of Authorization, (May 10, 2021), https://www.fda.gov/media/144412/download; see also Package Inserts 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.
[114] For example, data presented at the June 7, 2022 Meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) showed that in March 2022, unvaccinated people 12 years of age and older had 17 times higher COVID-19-associated death rates compared to those with a primary series and booster dose. It also showed that in March 2022, unvaccinated adults 18 years of age and older had a five times higher COVID-19-associated hospitalization rate compared with those who were fully vaccinated with an additional or booster dose. CDC, COVID-19 Epidemiology and Vaccination Rates in the United States at slides 20-21 (June 7, 2022), https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-7-2022-meeting-announcement#event-materials.
[115] FDA, Vaccine Safety Questions and Answers, last updated March 2018, https://www fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[116] Brown, et al., Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings - Barnstable County, Massachusetts, July 2021, Morb Mortal Wkly Rep. (Aug. 6, 2021), 70(31): 1059-1062, doi: 10.15585/mmwr mm7031e2.; Shitrit, et al., Nosocomial Outbreak Caused by the SARS-CoV-2 Delta Variant in a Highly Vaccinated Population, Israel, July 2021, Euro Surveill. (Sept. 2021), 26(39): 2100822, doi: 10.2807/1560-7917.ES.2021.26.39.2100822.

SARS-CoV-2 virus shedding duration[117] and a study evaluating whether vaccine-induced immune responses reduce nasal viral RNA burden or the titer of infectious SARS-CoV-2 in people infected despite vaccination relative to unvaccinated persons.[118] None of these studies conclude that the rate of infection is the same amongst vaccinated and unvaccinated individuals, as Petitioner suggests these studies show.

Thus, to the extent that the Petition asserts that the risk-benefit criterion for issuance of EUAs is no longer met on the basis of the evidence put forward in the Petition regarding rates of infection, we disagree. The Petition has not shown that the rates of infection among vaccinated individuals undermine FDA's conclusion that the known and potential benefits of the vaccine outweigh the known and potential risks when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12-15 years of age.

c. Effectiveness Against Emerging Variants

In addition, Petitioner argues that currently, in the 12-15 years of age population, the Pfizer-BioNTech COVID-19 Vaccine "barely meets the FDA's 50% [vaccine effectiveness] threshold"[119] and contends that this is, in large part, because "prior mRNA vaccination imprints serological responses toward [only] Wuhan-Hu-1 rather than variant antigens."[120] In support of this argument, Petitioner cites several articles for the proposition that vaccine effectiveness wanes over time and/or against certain variants and argues that "[t]his dramatic waning in efficacy…, the need for more doses, and the extremely limited benefit only further emphasize the necessity of revoking the EUA for children ages 12-15."[121] Petitioner also points to actions FDA took with respect to certain authorized monoclonal antibody treatments, arguing that if it is the Agency's policy "to revoke the EUA status of COVID-19 treatments that were formulated to be

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[117] Takahashi, et al., Duration of Infectious Virus Shedding by SARS-CoV-2 Omicron Variant–Infected Vaccinees, Emerg Infect Dis. (May 2022), 28(5): 998-1001, doi: https://doi.org/10.3201/eid2805.220197.

[118] Kasen, et al., Shedding of Infectious SARS-CoV-2 Despite Vaccination, medRxiv (Nov. 6, 2021), preprint: 2021.07.31.21261387, doi: https://doi.org/10.1101/2021.07.31.21261387.

[119] Petition 11. While Petitioner appears to refer to the recommendation in FDA's Vaccine Development and Licensure Guidance regarding the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial as the "threshold for EUA licensure," we note that there is no numeric effectiveness threshold specified in the criteria for issuance of an EUA. Section 564(c) of the FD&C Act.

[120] Id. at 11 (alteration in original). Petitioner quotes an article published in *Cell* for the proposition that prior mRNA vaccination imprints serological responses toward Wuhan-Hu-1 rather than variant antigens. See Röltgen, et al., Immune Imprinting, Breadth of Variant Recognition, and Germinal Center Response in Human SARS-CoV-2 Infection and Vaccination, Cell (Mar. 17, 2022),185(6): 1025-1040.e14, doi: 10.1016/j.cell.2022.01.018. FDA has considered the issues raised in this article, but we do not agree with Petitioner's contention that it establishes that the Pfizer-BioNTech COVID-19 Vaccine "barely meets the FDA's 50% [vaccine effectiveness] threshold." Petition at 11. Recent evidence supports the continuing effectiveness of the Pfizer-BioNTech COVID-19 Vaccine, particularly against more serious outcomes. See, e.g., CDC, COVID-19 Epidemiology and Vaccination Rates in the United States at 20-21 (June 7, 2022), https://www fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-7-2022-meeting-announcement#event-materials. Further, we note that FDA has recognized the importance of issues related to the optimal strain composition for COVID-19 vaccines to address current and emerging SARS-CoV-2 variants and when and how frequently to consider composition changes to address variants, and convened a meeting of the VRBPAC in April 2022 to discuss these and other questions. See FDA, Vaccines and Related Biological Products Advisory Committee April 6, 2022 Meeting Announcement, https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-april-6-2022-meeting-announcement#event-materials.

[121] Petition at 11-13.

effective against earlier variants, then the EUA for the Pfizer vaccine must likewise be revoked."[122] These arguments fail to show that the criterion for issuance of the EUA (i.e., that the known and potential benefits no longer outweigh the known and potential risks) is no longer met.

First, as explained above, it is important to understand that a COVID-19 vaccine need not be 100% effective in preventing COVID-19, or even close to 100% effective in doing so, in order to have a significant effect in altering the course of the COVID-19 pandemic and for the known and potential benefits to outweigh the known and potential risks.

In addition, we note that throughout the pandemic, FDA has made decisions based on the best available science as the SARS-CoV-2 virus has continued to evolve. The Pfizer-BioNTech COVID-19 Vaccine is an mRNA vaccine based on the original Wuhan strain (as is the other authorized mRNA vaccine: the Moderna COVID-19 Vaccine). Recently and currently circulating SARS-CoV-2 variants harbor mutations in the S protein that confer at least partial antigenic escape from vaccine-elicited immunity. Nonetheless, available data indicate that both of the authorized mRNA COVID-19 vaccines, have retained some level of effectiveness against all epidemiologically important SARS-CoV-2 variants that have emerged to date, with higher level effectiveness preserved against more serious outcomes (hospitalization and death) than against mild symptomatic disease.[123]

Results from observational studies that have investigated the effectiveness of the primary vaccination series of the Pfizer-BioNTech COVID-19 Vaccine have shown decreased

[122] Id. at 13.

[123] See CDC, COVID-19 Epidemiology and Vaccination Rates in the United States at 20-21 (June 7, 2022), https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-7-2022-meeting-announcement#event-materials; Lauring, et al., Clinical Severity of, and Effectiveness of mRNA Vaccines Against, Covid-19 from Omicron, Delta, and Alpha SARS-CoV-2 Variants in the United States: Prospective Observational Study, BMJ (2022), 376 :e069761, doi:10.1136/bmj-2021-069761; Andrews, et al., Covid-19 Vaccine Effectiveness Against the Omicron (B.1.1.529) Variant, NEJM (Apr. 21, 2022), 386: 1532-1546, DOI: 10.1056/NEJMoa2119451; Taylor, et al., COVID-19–Associated Hospitalizations Among Adults During SARS-CoV-2 Delta and Omicron Variant Predominance, by Race/Ethnicity and Vaccination Status — COVID-NET, 14 States, July 2021–January 2022, Morb Mortal Wkly Rep. (Mar. 25, 2022), 71(12): 466–473, DOI: https://www.cdc.gov/mmwr/volumes/71/wr/mm7112e2 htm; Stowe, et al., Effectiveness of COVID-19 Vaccines Against Omicron and Delta Hospitalisation: Test Negative Case-Control Study, medRxiv (Apr. 01, 2022), Preprint: 2022.04.01.22273281, doi: https://doi.org/10.1101/2022.04.01.22273281; Ferdinands, et al., Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021–January 2022, Morb Mortal Wkly Rep. (Feb. 18, 2022), 71(7): 255–263, DOI: https://www.cdc.gov/mmwr/volumes/71/wr/mm7107e2.htm; Tenforde, et al., Effectiveness of a Third Dose of Pfizer-BioNTech and Moderna Vaccines in Preventing COVID-19 Hospitalization Among Immunocompetent and Immunocompromised Adults — United States, August–December 2021, Morb Mortal Wkly Rep. (Jan. 28, 2022), 71(4);118–124, DOI: https://www.cdc.gov/mmwr/volumes/71/wr/mm7104a2 htm; Tseng, et al., Effectiveness of mRNA-1273 Against SARS-CoV-2 Omicron and Delta Variants, Nature Medicine (Feb 21, 2022), 28: 1063-1071, https://doi.org/10.1038/s41591-022-01753-y.

effectiveness against certain variants (notably Omicron) and waning effectiveness over time.[124] Data have shown that first booster doses have restored waning vaccine effectiveness, including against severe disease and hospitalization associated with Omicron,[125] although observational studies have also indicated waning effectiveness of the first booster dose over time, mainly against mild disease, with some studies also suggesting waning effectiveness against hospitalization[126] and lower effectiveness among the immunocompromised.[127]

Several of the articles cited by Petitioner as evidence of reduced effectiveness of the Pfizer-BioNTech COVID-19 Vaccine against certain variants are generally consistent with FDA's analysis.[128] While some of the cited articles suggest a potentially greater reduction in protection against COVID-19 than others, they do not establish that, the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine have decreased, such that they no longer outweigh the known and potential risks. [129] Therefore, the totality of the available scientific evidence continues

[124] See Andrews, et al., Covid-19 Vaccine Effectiveness Against the Omicron (B.1.1.529) Variant, 2022; Taylor, et al., COVID-19–Associated Hospitalizations Among Adults During SARS-CoV-2 Delta and Omicron Variant Predominance, by Race/Ethnicity and Vaccination Status — COVID-NET, 14 States, July 2021–January 2022, 2022.

[125] See Andrews, et al., Covid-19 Vaccine Effectiveness Against the Omicron (B.1.1.529) Variant, 2022; Taylor, et al., COVID-19–Associated Hospitalizations Among Adults During SARS-CoV-2 Delta and Omicron Variant Predominance, by Race/Ethnicity and Vaccination Status — COVID-NET, 14 States, July 2021–January 2022, 2022.

[126] Stowe, et al., Effectiveness of COVID-19 Vaccines Against Omicron and Delta Hospitalisation: Test Negative Case-Control Study, 2022; Ferdinands, et al., Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021–January 2022, 2022; Chemaitelly, et al., Duration of mRNA Vaccine Protection Against SARS-CoV-2 Omicron BA.1 and BA.2 Subvariants in Qatar, Nature Communications, 12:3082, 2022, https://doi.org/10.1038/s41467-022-30895-3.

[127] Tenforde, et al., Effectiveness of a Third Dose of Pfizer-BioNTech and Moderna Vaccines in Preventing COVID-19 Hospitalization Among Immunocompetent and Immunocompromised Adults — United States, August–December 2021, Morb Mortal Wkly Rep. (Jan. 28, 2022), 71:118–124. DOI:http://dx.doi.org/10.15585/mmwr mm7104a2.

[128] Klein, et al., Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA Vaccination in Preventing COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Nonimmunocompromised Children and Adolescents Aged 5–17 Years — VISION Network, 10 States, April 2021–January 2022, Morb Mortal Wkly Rep. (Mar. 4 2022), 71(9): 352–358, https://www.cdc.gov/mmwr/volumes/71/wr/mm7109e3 htm.; Tartof, et al., Durability of BNT162b2 Vaccine Against Hospital and Emergency Department Admissions due to the Omicron and Delta Variants in a Large Health System in the USA: A Test-Negative Case-Control Study, The Lancet Respiratory Medicine (Apr. 22, 2022), S2213-2600(22)00101-1, doi:10.1016/S2213-2600(22)00101-1.; Fowlkes, et al., Effectiveness of 2-Dose BNT162b2 (Pfizer BioNTech) mRNA Vaccine in Preventing SARS-CoV-2 Infection Among Children Aged 5–11 Years and Adolescents Aged 12–15 Years — PROTECT Cohort, July 2021–February 2022, Morb Mortal Wkly Rep. (Mar. 18, 2022), 71(11): 422–428, https://www.cdc.gov/mmwr/volumes/71/wr/mm7111e1.htm.; Dorabawila, et al., Effectiveness of the BNT162b2 Vaccine Among Children 5-11 and 12-17 Years in New York After the Emergence of the Omicron Variant, medRxiv (Feb. 2022), 2022.02.25.22271454, doi: https://doi.org/10.1101/2022.02.25.22271454.

[129] See Regev-Yochay, et al., Letter to the Editor, Efficacy of a Fourth Dose of COVID-19 mRNA Vaccine against Omicron N. Engl. J. Med. (Apr. 7, 2022), 386: 1377-1380, DOI: 10.1056/NEJMc2202542 (summarizing open label study where "[v]accine efficacy was estimated to be higher for the prevention of symptomatic disease (43% for BNT162b2 and 31% for mRNA-1273)"). This letter does not provide separate estimates of efficacy for serious and mild disease. See also Subramanian, et al., Increases in COVID-19 Are Unrelated to The Levels of Vaccination Across 68 Countries and 2947 Counties in the United States, Euro. Journal of Epidemiology (Sept. 2021), 36:1237-

to support our determination that the Pfizer-BioNTech COVID-19 Vaccine's known and potential benefits outweigh its known and potential risks for individuals 12-15 years of age. The Petition does not provide evidence showing otherwise.

With respect to Petitioner's arguments regarding monoclonal antibody treatments, we disagree that revision of the EUAs for certain of these treatments indicates that revocation of the EUA for the Pfizer-BioNTech COVID-19 Vaccine—a different product with different data available regarding its known and potential benefits and risks, and a different context of use—is warranted. At this time, FDA has not, as Petitioner suggests, revoked the EUAs for the monoclonal antibody treatments referenced in the Petition but has revised the authorizations to add limitations on their authorized use, including the following:

- On January 24, 2022, FDA revised the EUAs for two monoclonal antibody treatments – bamlanivimab and etesevimab (administered together) and REGEN-COV (casirivimab and imdevimab) – so that they are not authorized for use in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant, based on available information, including variant susceptibility to the drugs and regional variant frequency. Because data showed these treatments are highly unlikely to be active against the Omicron variant, which was estimated, based on CDC data, to account for more than 99% of U.S. cases, FDA also announced that these treatments were not authorized for use anywhere in the United States. FDA noted that it would continue to monitor conditions and that in the future, if patients in certain geographic regions are likely to be infected or exposed to a variant that is susceptible to these treatments, then use of these treatments may be authorized in these regions.[130]

- On February 23, 2022, FDA similarly revised the EUA for sotrovimab so that use of this treatment is not authorized in geographic regions where infection is likely to have been caused by a variant that is not susceptible to this treatment. FDA has continued to monitor conditions to determine whether use in a geographic region is consistent with the scope of authorization. As of April 5, 2022, Sotrovimab is not authorized to treat COVID-19 in any U.S. region due to increases in the proportion of COVID-19 cases caused by the Omicron BA.2 sub-variant.[131]

As FDA explained, these actions were informed by its careful analysis of data indicating that the monoclonal antibody treatments were unlikely to be effective against a variant or sub-variant in

1240, https://www ncbi nlm nih.gov/pmc/articles/PMC8481107/pdf/10654_2021_Article_808.pdf (finding that on a "country-level, there appears to be no discernable relationship between the percentage of population fully vaccinated and new COVID-19 cases in the last 7 days [preceding September 3, 2021]"). This analysis from a one-week time period does not state how it addressed numerous factors, including differences between countries in terms of testing and timing of vaccine availability, as well as differences in which vaccines were available.

[130] FDA, Coronavirus (COVID-19) Update: FDA Limits Use of Certain Monoclonal Antibodies to Treat COVID-19 Due to the Omicron Variant (Jan. 24, 2022), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-certain-monoclonal-antibodies-treat-covid-19-due-omicron.

[131] FDA, FDA updates Sotrovimab emergency use authorization (Apr. 5, 2022), https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization.

wide circulation.[132] Scientifically, it is appropriate for FDA to take different approaches to the authorizations of monoclonal antibodies compared to vaccines. Monoclonal antibodies authorized for the treatment of COVID-19 bind to specific small structural features of the virus which can change in a new variant, whereas vaccines elicit a polyclonal response against the vaccine antigen, in this case the S protein of SARS-CoV-2. Thus, the immune response elicited by vaccination can be cross protective even as novel viral variants emerge. While there are data suggesting a reduction of protection against COVID-19 after the second dose of the Pfizer-BioNTech COVID-19 Vaccine in all authorized populations, including individuals 12-15 years of age, as explained above, available data indicate that the vaccine has retained some level of effectiveness against all epidemiologically important SARS-CoV-2 variants that have emerged to date, with higher level effectiveness preserved against more serious outcomes. Moreover, FDA evaluates the totality of available scientific evidence to determine if the known and potential benefits outweigh the known and potential risks. The totality of the available scientific evidence is specific to each product, and thus FDA's past decisions regarding EUAs for monoclonal antibody treatments do not dictate its decisions regarding the EUA for the Pfizer-BioNTech COVID-19 Vaccine.

Therefore, to the extent that the Petition asserts that the risk-benefit criterion for issuance of EUAs is no longer met on the basis of emerging variants, we disagree. The Petition has not shown that the impacts of emerging variants undermine FDA's conclusion that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks when used for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12-15 years of age.

d. Post-Authorization Safety

Petitioner identifies several concerns related to post-authorization safety and argues that "[e]ven if [the Pfizer-BioNTech COVID-19 Vaccine] had maintained VE reasonably close to the 100% efficacy it claimed in its trial, the EUA should still be revoked in light of the real-world safety issues that have been identified since its authorization in 12- to 15-year-olds."[133]

Background on Passive and Active Surveillance

Because the Petition includes several arguments related to COVID-19 vaccine surveillance systems and activities, we provide below a summary of vaccine safety surveillance.

[132] Petitioner argues that if FDA limited the authorized use of these treatments where "waning efficacy" is "theoretical," then it should revoke the EUA for the Pfizer-BioNTech COVID-19 Vaccine for which "waning efficacy is proven." Petition at 13. To the extent Petitioner argues that the Pfizer-BioNTech COVID-19 Vaccine has been "proven" not to be effective, such that it would fail to satisfy the criterion in section 564(c)(2)(A) of the FD&C Act and that its known and potential benefits would not weigh its risks, FDA is not aware of any data showing that the Pfizer-BioNTech COVID-19 Vaccine is not effective, nor has Petitioner provided such information.

[133] Petition at 14.

- *Passive Surveillance*

The Vaccine Adverse Event Reporting System (VAERS) is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed or authorized in the United States. Passive surveillance is defined as unsolicited reports of adverse events that are sent to a central database or health authority. In the United States, these are received and entered into VAERS, which is co-managed by FDA and CDC. In the current pandemic, these reports are being used to monitor the occurrence of both known and unknown adverse events, as providers of COVID-19 vaccines are required to report serious adverse events to VAERS. As part of FDA and CDC's multi-system approach to post-licensure and post-authorization vaccine safety monitoring, VAERS is designed to rapidly detect unusual or unexpected patterns of adverse events. VAERS reports generally cannot be used to determine if a vaccine caused or contributed to an adverse event or illness. If the VAERS data suggest a possible link between an adverse event and vaccination, the relationship may be further studied in a controlled fashion.[134]

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

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

If VAERS monitoring suggests that a vaccine might be causing a health problem, additional scientifically rigorous studies or investigations can be performed by FDA and CDC. Monitoring and analysis of VAERS reports typically includes ongoing screening of all incoming serious reports for COVID-19 vaccines (including collection of follow-up medical information and in-depth medical review of certain adverse event reports of interest), statistical data mining techniques, and epidemiological analysis. We look for patterns and similarities in the onset timing and clinical description. literature to identify other reports with similar event patterns and clinical description and to understand possible biologic hypotheses that could plausibly link the reported adverse event to the vaccine. We review the pre-licensure or pre-authorization data and any other post-marketing studies that have been conducted. We also consider "background rate," meaning the rate at which a medical event occurs in the unvaccinated general population. When necessary, we discuss the potential adverse event with our federal and international safety surveillance partners. We also carefully evaluate unusual or unexpected reports, as well as reports of "positive re-challenges" (adverse events that occur in the same patient after each dose received).

[134] FDA, VAERS Overview, https://www.fda.gov/vaccines-blood-biologics/vaccine-adverse-events/vaers-overview.

When there is sufficient evidence for a potential safety concern, we may proceed to conduct large studies, and we may coordinate with our federal, academic, and private partners to further assess the potential risk after vaccination. In addition, when potential safety issues arise, they are often presented to various U.S. government advisory committees, including the Vaccines and Related Biological Products Advisory Committee (VRBPAC), the Advisory Committee on Immunization Practices (ACIP), and the Advisory Committee on Childhood Vaccines, and are often discussed with experts from other countries and from the World Health Organization. Federal agencies that assist in population-based vaccines safety studies include the CDC, Centers for Medicaid and Medicare (CMS), the Department of Defense (DoD), and the Indian Health Services (IHS). In addition, we generally communicate and work with international regulatory authorities and international partners to conduct studies in vaccine safety.

- *Active Surveillance*

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

BEST: To elaborate further, the BEST system,[135] which is part of the Sentinel initiative,[136] comprises large-scale claims data, electronic health records (EHR), and linked claims-EHR databases with a data lag of approximately three months. The system makes use of multiple data sources and enables rapid queries to detect or evaluate adverse events as well as studies to answer specific safety questions for vaccines. The linked claims-EHR database makes it possible to study the safety of vaccines in sub-populations with pre-existing conditions or in pregnant women. The major partners for BEST currently are Acumen, IBM Federal HealthCare, IQVIA, and Columbia University and many affiliated partners such as MedStar Health, BlueCross BlueShield of America, the Observational Health Data Sciences and Informatics (OHDSI), OneFlorida, University of California and several others.[137]

CMS: FDA has worked over the past several years with CMS to develop capabilities for routine and time-sensitive assessments of the safety of vaccines for people 65 years of age and older

[135] FDA, CBER Biologics Effectiveness and Safety (BEST) System, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system.
[136] FDA, FDA's Sentinel Initiative, https://www fda.gov/safety/fdas-sentinel-initiative.
[137] To confirm the utility of the BEST system for situations such as COVID-19 vaccine surveillance, a test case was conducted. This study aimed to replicate a previous study by the CDC's Vaccine Safety Datalink (VSD) (Klein, et al., Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures, Pediatrics (Jul. 2010), 126(1):e1-8, doi: 10.1542/peds.2010-0665.) that examined the databases and analytic capabilities of the new system. The objective of this study was to test the new system's ability to reproduce the increased risk of febrile seizures in children receiving the first dose of measles-mumps-rubella-varicella (MMRV) vaccine, compared to that of MMR and varicella vaccines separately but on the same day. The results of the study met the objectives and demonstrated the ability of the BEST Initiative data network to run a complex study protocol at multiple sites using a distributed data network and the Observational Medical Outcomes Partnership Common Data Model (organizing disparate data sources into the same database design using a common format).

using the Medicare Claims database.[138] Because it was already in place, this system was immediately put into use for COVID-19 vaccine surveillance to monitor for adverse events.[139] During the current pandemic, FDA, CMS, and CDC have used the Medicare data to publish a study showing that frailty, comorbidities, and race/ethnicity were strong risk factors of COVID-19 hospitalization and death among the U.S. elderly.[140]

VSD: In addition, the Vaccine Safety Datalink (VSD) is a collaborative project between CDC's Immunization Safety Office and nine health care organizations. As noted on the CDC's webpage, the VSD started in 1990 and continues today in order to monitor safety of vaccines and conduct studies about rare and serious adverse events following immunization.

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

The VSD has a long history of monitoring and evaluating the safety of vaccines. Since 1990, investigators from the VSD have published many studies to address vaccine safety concerns.[141]

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

Petitioner's Arguments Regarding VAERS Data

In arguing that the EUA for the Pfizer-BioNTech COVID-19 Vaccine should be revoked for use in individuals 12-15 years of age due, in part, to safety concerns, Petitioner asserts that the number of reported adverse events "following COVID-19 vaccines … alone should necessitate

[138] CMS, Standard Analytical Files (Medicare Claims) – LDS, https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/StandardAnalyticalFiles.
[139] As one example of the capabilities of this system, FDA, CMS, and CDC evaluated the risk of Guillain-Barré syndrome (GBS) following influenza vaccination after CDC's Vaccine Safety Datalink, identified safety signals suggesting an increased risk of GBS following high-dose influenza vaccinations and Shingrix vaccinations during the 2018-2019 influenza season. CBER, CDC, and CMS formed working groups in February 2019 to refine these safety signals in the CMS data.
[140] Izurieta, et al., Natural History of Coronavirus Disease 2019: Risk Factors for Hospitalizations and Deaths Among >26 Million US Medicare Beneficiaries, The Journal of Infectious Diseases (Mar. 15, 2021), 223(6): 945–956, https://doi.org/10.1093/infdis/jiaa767.
[141] See, e.g., CDC, White Paper on the Safety of the Childhood Immunization Schedule, Vaccine Safety Datalink, https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf.

revocation of the EUA."[142] Petitioner points to a National Vaccine Information Center webpage to show that, "VAERS data as of May 6, 2022, shows a total of 31,549 adverse events reported in 12- to 17-year-olds, of which 1,812 were rated as serious and 44 were deaths."[143] We also note that the Petition refers to a letter that appears to have been submitted to ACIP in November 2021 for the proposition that "[t]he sheer amount of VAERS reports is an *abnormal* finding and a clear 'Safety Signal' that is being *knowingly* and *willfully* ignored by the CDC and FDA."[144] However, Petitioner has not provided any evidence showing that FDA is ignoring safety signals regarding COVID-19 vaccines.

There are extensive vaccine safety surveillance efforts in place, including VAERS, for COVID-19 vaccines.[145] VAERS reports provide a very important tool in monitoring vaccine safety, but these reports alone cannot be used to determine if a vaccine caused or contributed to an adverse event or illness.[146] Nonetheless, there are particular limitations in interpreting VAERS reports for COVID-19 vaccines. For example, under the EUAs for the Authorized COVID-19 vaccines, unlike for previously approved vaccines, vaccination providers are required to report to VAERS serious adverse events following vaccination with the COVID-19 vaccines "irrespective of attribution to vaccination" and regardless of how long after vaccination the adverse event occurs.[147]

It is also important to consider other factors that have contributed to the volume of VAERS reports. First, we note the large number of COVID-19 vaccine doses have been administered in the United States. As of June 14, 2022, over 591,000,000 doses of authorized or approved

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[142] Petition at 16.

[143] Id. In addition, the Petition states without attribution that there have been "1,790 reported vaccine-related hospitalizations among children ages 6-17 years old." Id. As noted above, VAERS is not designed to assess causality. Therefore, it does not appear that reports of "vaccine-related hospitalizations" refers to data from VAERS. Without any indication of the source of Petitioner's numbers, we cannot assess them, and they do not provide a basis to alter our determination that known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 12-15 years of age outweigh the known and potential risks.

[144] Id. (emphasis in original and internal quotations omitted). The letter referenced in the Petition states, "As of October 15, 2021, 123 deaths attributed to the Covid vaccines are now listed for the 0-24 age group category in VAERS, 52 of which are in the 0-18 age group. This is an appalling and *abnormal* finding and a clear "Safety Signal" that is being *knowingly* and *willfully* ignored by the ACIP committee to date." Petition, Attachment 5 (Sources Part 5), at 82. The letter does not provide any support for identifying these deaths as "attributed to" COVID-19 vaccines. The source it provides for these numbers is https://openvaers.org, which states "OpenVAERS is a private organization that posts publicly available CDC/FDA data of injuries reported post-vaccination. Reports are not proof of causality."

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

[146] VAERS Data Disclaimer, https://vaers hhs.gov/data html

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

COVID-19 Vaccines have been administered.[148] Another contributing factor is the v-safe system,[149] which is a CDC smartphone-based active-surveillance system, developed for the COVID-19 vaccination program, in which participants who have been vaccinated may voluntarily enroll. V-safe sends text messages and web surveys to participants who can report side effects following receipt of a COVID-19 vaccine. If a participant indicates through the v-safe surveys that he or she required medical care at any time, CDC calls the participant to complete a report through VAERS. This system is unique to COVID-19 vaccines and may be contributing to the number of VAERS reports submitted for the COVID-19 Vaccines.

Finally, an additional potential factor is the concept of "stimulated reporting."[150] Because of extensive media coverage and awareness of the public health emergency—and of COVID-19 Vaccines and their reported side effects–vaccine recipients, health care providers, and others may be more likely to report adverse events for the COVID-19 vaccines than for other vaccines that have been widely available for longer periods of time. Although VAERS is not designed to assess causality, FDA and CDC actively monitor VAERS reports and engage in additional studies or investigations if VAERS monitoring suggests that a vaccine might be causing a health problem.

Petitioner's arguments fail to take the factors outlined above into account. Thus the "sheer amount" of reports to VAERS do not provide support for the Petitioner's claim that FDA is "knowingly and willfully" ignoring VAERS safety signals. While the Petition claims that this "sheer amount" of reports to VAERS means that FDA should revoke the EUA for the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 12-15 years old, we disagree. The Petition's arguments regarding the "sheer amount" of reports do not demonstrate 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 12-15 years of age.

Petitioner's Arguments Regarding Other Surveillance Data

Petitioner also cites analyses of v-safe and Coronavirus Disease 2019–Associated Hospitalization Surveillance Network (COVID-NET) data for the proposition that the "government's own data suggests the benefits of mass vaccination do not outweigh their risks."[151] However, the publications Petitioner cites do not support this assertion. Petitioner points to an analysis of COVID-19 vaccine safety in adolescents using VAERS and v-safe data, which found that 25.4% of enrollees ages 12-15 reported "any health impact" within 0-7 days of receiving their second

[148] CDC, COVID Data Tracker, COVID-19 Vaccinations in the United States, https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total (accessed June 14, 2022).
[149] CDC, v-safe Overview, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe html.
[150] "Like all spontaneous public health reporting systems, VAERS has limitations. VAERS is subject to reporting bias, including underreporting of adverse events – especially common, mild ones– and stimulated reporting, which is elevated reporting that might occur in response to intense media attention and increased public awareness, such as during the 2009 H1N1 pandemic influenza vaccination program" Shimabukuro, et al., Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), Vaccine (Nov. 4, 2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/. See also Vellozzi, et al., Adverse Events Following Influenza A (H1N1) 2009 Monovalent Vaccines Reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009–January 31, 2010, Vaccine (Oct. 21, 2010), https://www.sciencedirect.com/science/article/pii/S0264410X10013319.
[151] Petition at 16.

dose of the Pfizer-BioNTech COVID-19 Vaccine.[152] Of those, 0.04% reported hospitalization.[153] Petitioner appears to contrast this with an analysis of COVID-19 hospitalizations among children and adolescents using a different data set from COVID-NET, which found a cumulative incidence of COVID-19-associated hospitalizations of 49.7 per 100,000 children and adolescents during March 1, 2020-August 14, 2021,[154] in an attempt to show that the "benefits of mass vaccination do not outweigh their risks."[155] However, the Petition fails to explain the connection Petitioner draws between these two analyses and thus fails to support its argument.

We note that to the extent Petitioner is arguing that the numbers reported in these two publications can be directly compared to determine if the known and potential benefits of the vaccine outweigh its known and potential risks, this is not sound. Such an approach would fail, for example, to account for differences between the v-safe and COVID-NET data sets. In addition, v-safe does not record reason for hospitalization; thus, it cannot be determined whether hospitalizations reported by v-safe enrollees were related to vaccination.[156]

Thus, the Petition's reliance on the cited data fails to demonstrate that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine no longer outweigh the known and potential risks.

Petitioner's Arguments Regarding Myocarditis and Pericarditis

In raising questions about the benefit-risk profile of the vaccine, Petitioner identifies reports of "heart damage, including myocarditis" as the "most notabl[e]" reports of adverse events following vaccination with the Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age and argues that the risks of myocarditis and pericarditis outweigh the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine in this age group.[157] While FDA has carefully considered risk of myocarditis and pericarditis for vaccine recipients, including those 12-15 years of age, we have concluded that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine for this age group outweigh the known and potential risks. For the reasons described below, the Petition does not provide information that changes this conclusion.

As noted above, adverse event reports following administration of a COVID-19 vaccine are reviewed to assess possible safety concerns. Post-authorization safety surveillance reports received by FDA and CDC for the Pfizer-BioNTech COVID-19 Vaccine identified increased

[152] Hause, et al., COVID-19 Vaccine Safety in Adolescents Aged 12–17 Years — United States, December 14, 2020–July 16, 2021, Morb Mortal Wkly Rep. (Aug. 6, 2021), 70(31): 1053-1058, DOI: http://dx.doi.org/10.15585/mmwr.mm7031e1.
[153] Id.
[154] Delahoy, et al., Hospitalizations Associated with COVID-19 Among Children and Adolescents — COVID-NET, 14 States, March 1, 2020–August 14, 2021, Morb Mortal Wkly Rep. (Sep. 10, 2021), 70(36): 1255–1260, DOI: http://dx.doi.org/10.15585/mmwr.mm7036e2external icon.
[155] Petition at 16.
[156] Hause, et al., COVID-19 Vaccine Safety in Adolescents Aged 12–17 Years — United States, December 14, 2020–July 16, 2021, 2021.
[157] Petition at 14.

risks of myocarditis and pericarditis, particularly within seven days following administration of the second dose of the two-dose primary series. On June 25, 2021, FDA announced revisions to the patient and provider fact sheets for the Pfizer-BioNTech COVID-19 Vaccine, including the addition of a warning about myocarditis and pericarditis to the Fact Sheet for Healthcare Providers Administering Vaccine.[158]

FDA has continued to monitor data related to risk of myocarditis and pericarditis in vaccine recipients since that announcement. Reporting rates for medical chart-confirmed myocarditis and pericarditis in VAERS have been higher among adult males under 40 years of age than among females and older males, and have been highest in males 16-17 years of age.[159] Although some cases of vaccine-associated myocarditis/pericarditis have required intensive care support, available short-term data suggest that most individuals have had resolution of symptoms with conservative management.[160]

Petitioner calls into question FDA's assessment of the risk of myocarditis and pericarditis. Citing a benefit-risk assessment presented by FDA at the October 26, 2021 meeting of the VRBPAC,[161] Petitioner asserts that FDA "utilized an "inciden[ce] rate of only 106 cases of myopericarditis cases per million children 5 to 15[.]"[162] The Petition then points to an analysis of data from the Kaiser Permanente Northwest health system ("KPNW Analysis") for the proposition that the "true incidence of myopericarditis" is actually 208 cases per million and "markedly higher than the incidence reported to US advisory committees[.]"[163] However, the Petitioner does not show that FDA has relied on incorrect data when determining that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its known and potential risks.

The FDA benefit-risk assessment Petitioner cites models different scenarios based on different estimates of model inputs (e.g., COVID-19 related incidence rates, vaccine effectiveness, incidence of excess myocarditis/pericarditis, rate of hospitalization and ICU stay due to vaccine-related myocarditis/pericarditis).[164] We note that this FDA presentation to the VRBPAC specifically recognized "large variation on the incidence of excess myocarditis cases among

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[158] FDA, Coronavirus (COVID-19) Update: June 25, 2021, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-june-25-2021.

[159] See CDC, Vaccines and Related Biological Products Advisory Committee, Update on myocarditis following mRNA COVID-19 vaccination, at slide 10 (June 14, 2022), https://www fda.gov/media/159228/download; CDC, CDC Advisory Committee on Immunization Practices, Updates on safety of COVID-19 primary series in children and adolescents ages 5–11 and 12–15 years, and booster doses in adolescents ages 16–24, (January 5, 2022), https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-01-05/02-COVID-Su-508.pdf.

[160] CDC, CDC Advisory Committee on Immunization Practices, Updates on safety of COVID-19 booster dose (slide presentation). April 20, 2022. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-04-20/03-COVID-Klein-Shimabukuro-508.pdf; Oster, et al., Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021, JAMA (Jan. 2022).

[161] FDA, Benefits-Risks of Pfizer-BioNTech COVID-19 Vaccine for Ages 5 to 11 Years (Oct. 26, 2021), https://www.fda.gov/media/153507/download.

[162] Petition at 14-15.

[163] Id. at 15.

[164] FDA-Benefits-Risks of Pfizer-BioNTech COVID-19 Vaccine for Ages 5 to 11 Years, (Oct. 26, 2021), https://www.fda.gov/media/153507/download.

different data sources (such as OPTUM, [Vaccine Safety Datalink (VSD),] and VAERS)."[165] For rare events, it is not unexpected to see such variation in incidence rates across data sources.

With regard to the KPNW Analysis, the authors sought to compare the risk of myopericarditis identified using a health record encounter text analysis they developed ("encounter methodology") with the risk identified using the VSD Rapid Cycle Analysis methodology.[166] As noted above, the VSD is a collaborative project between CDC's Immunization Safety Office and nine health care organizations. The VSD uses electronic health data from each participating site and conducts vaccine safety studies based on questions or concerns raised from the medical literature and reports to VAERS. Rapid Cycle Analysis allows VSD to detect elevated rates of adverse events following vaccination in near real time so the public can be informed quickly of possible risks. Using VSD data that are updated each week, the rates of adverse events that occur in people who have received a particular vaccine are compared to the rate of adverse events that occurs in a similar group of people who have not received that vaccine.[167]

Based on an analysis of health records for patients who received at least one dose of an mRNA vaccine during a specified time period, the authors of the KPNW Analysis conclude that their encounter methodology "identified additional valid cases of myopericarditis following an mRNA vaccination that would be missed by the VSD's search algorithm [and that] [t]he true incidence of myopericarditis is markedly higher than the incidence reported to US advisory committees in the fall of 2021."[168] However, regardless of whether the authors accurately conclude that their methodology identified myopericarditis cases that the VSD Rapid Cycle Analysis would miss or be more delayed in identifying, this does not demonstrate that FDA has underestimated the risk of myocarditis and pericarditis among individuals 12-15 years of age.

VSD data are one of multiple sources of information that FDA considers when weighing the known and potential benefits and risks of a COVID-19 vaccine, and we believe VSD is a valuable data source. However, the fact that VSD data have been included in presentations made to the VRBPAC (which advises FDA but is not a decision-making body) and ACIP does not mean these data are the sole source of information regarding estimated incidence of myocarditis and pericarditis that informs FDA's decisions. For example, the benefit-risk assessment FDA presented at the October 26, 2021 VRBPAC meeting (that Petitioner cites) estimates excess myocarditis/pericarditis cases based on an analysis of OPTUM healthcare claims data.[169] FDA also considers the limitations of the available data on COVID-19 vaccine safety. Consistent with the statutory requirements for issuance of EUAs, FDA has made decisions about whether the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its known

[165] Id. at 5.
[166] Sharff, et al., Risk of Myopericarditis Following COVID-19 mRNA Vaccination in a Large Integrated Health System: A Comparison of Completeness and Timeliness of Two Methods, Pharmacoepidemiol Drug Saf. (Apr. 11, 2022), epub ahead of print, doi: 10.1002/pds.5439.
[167] CDC, Vaccine Safety Datalink (VSD), last reviewed August 2020, https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index html.
[168] Sharff, et al., Risk of Myopericarditis Following COVID-19 mRNA Vaccination in a Large Integrated Health System: A Comparison of Completeness and Timeliness of Two Methods (2022).
[169] FDA, Benefits-Risks of Pfizer-BioNTech COVID-19 Vaccine for Ages 5 to 11 Years, at 3, 5.

and potential risk based on the totality of the available scientific evidence [170] (section 564(c)(2)(B) of the FD&C Act).

Petitioner also asserts that "studies now confirm that the risk of cardiomyopathies in youth outweighs their risks for hospitalizations from COVID-19."[171] In support of this assertion, Petitioner again points to a letter that appears to have been submitted to ACIP in November 2021 and several sources cited therein for the following proposition: "In adolescent boys ages 12 to 15 with no medical comorbidities who received their second mRNA vaccine dose, 'the cardiac adverse event rate was 3.7 to 6.1 times higher, than their 120-day COVID-19 hospitalization risk as of August 21, 2021, and 2.6-4.3-fold higher at times of high weekly hospitalization risk.[172] Only one of the sources cited compares risk of post-vaccination myocarditis/pericarditis with risk of COVID-19 hospitalization.[173] Based on one of two methods the authors employed, this article estimates that "the myo/pericarditis risk for a 12–15-year-old boy without a comorbidity receiving his second dose of the vaccine is 2.8x higher than his 120-day risk of hospitalization even without adjusting for 40% incidental hospitalizations."[174,175] Notably, the article estimates that myocarditis/pericarditis risk was not higher than 120-day risk of hospitalization in all populations studied (e.g., "boys with at least one comorbidity and all girls appear to have a favorable benefit-risk ratio from vaccination during times of moderate to very high disease prevalence").[176] However, there are key limitations to the analyses employed by the authors, such as lack of confirmation with the reporting clinician for myocarditis/pericarditis reports obtained from VAERS and the fact that VAERS is a passive surveillance system, which is also subject to various biases. VSD and BEST, which are active surveillance systems, provide more reliable estimates of cases and the denominator vaccinated population. Therefore, this article does not establish that "the risk of cardiomyopathies in youth outweighs their risks for hospitalizations from COVID-19" as Petitioner claims.[177]

[170] For an extensive discussion of FDA's consideration of known and potential benefits and risks of the Pfizer-BioNTech COVID-19 Vaccine see FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda.
[171] Petition at 15.
[172] Id. at 15 n.76.
[173] Because the other sources Petitioner cites do not address whether "cardiac adverse event rate" is higher than COVID-19 hospitalization risk for individuals 12-15 years of age, they do not support the proposition for which Petitioner cites them.
[174] Krug, et al., BNT162b2 Vaccine-Associated Myo/Pericarditis in Adolescents: A Stratified Risk-Benefit Analysis, Eur J Clin Invest. (May 2022), 52(5): e13759, https://doi.org/10.1111/eci.13759.
[175] We note that the Preprint version of this article that was cited in the Petition stated that, "[f]or boys 12-15 without medical comorbidities receiving their second mRNA vaccination dose, the rate of [cardiac adverse event] is 3.7 to 6.1 times higher than their 120-day COVID-19 hospitalization risk as of August 21, 2021 (7-day hospitalizations 1.5/100k population) and 2.6-4.3-fold higher at times of high weekly hospitalization risk (7-day hospitalizations 2.1/100k), such as during January 2021." https://www medrxiv.org/content/10.1101/2021.08.30.21262866v1. However, this same language does not appear in the subsequently published version of the article. See Krug, et al., BNT162b2 Vaccine-Associated Myo/Pericarditis in Adolescents: A Stratified Risk-Benefit Analysis, 2022.
[176] Krug, et al., BNT162b2 Vaccine-Associated Myo/Pericarditis in Adolescents: A Stratified Risk-Benefit Analysis, 2022.
[177] Petition at 15. We note that petitioner appears to equate myocarditis/pericarditis with cardiomyopathy, but we do not view these terms as interchangeable.

In addition, the Petition claims that additional booster doses of the Pfizer-BioNTech COVID-19 Vaccine "carry an even greater risk of myocarditis and adverse events."[178] The article Petitioner cites in support of this proposition does not evaluate or state whether there is a greater risk of adverse events generally following an additional booster dose of the Pfizer-BioNTech COVID-19 Vaccine in individuals 12-15 years of age. Instead, the article states that the authors "observe[d] an increase in myocarditis events following a third dose of [Pfizer-BioNTech COVID-19] [V]accine [and that while] the incidence rate ratios are higher sequentially following each dose of mRNA vaccine, the risk remains small in the overall population with an estimated 2 additional cases of myocarditis per million following a booster dose of [Pfizer-BioNTech COVID-19 Vaccine]."[179] In males less than 40 years of age, the authors estimated an additional 13 myocarditis events following a third booster dose of the Pfizer-BioNTech COVID-19 Vaccine (compared with 12 following a second dose of the vaccine and 7 following a positive SARS-CoV-2 test). Particularly relevant to Petitioner's request, the article also acknowledges that "the number of myocarditis events was too small [in children 13-17 years of age] and precluded an evaluat[ion] of risk."[180] Therefore, we do not agree that this article demonstrates that booster doses of the Pfizer-BioNTech COVID-19 Vaccine "carry an even greater risk of myocarditis and adverse events." In addition, we note that an analysis of VAERS data presented at the April 20, 2022 ACIP meeting found that VAERS reporting rates of myocarditis in individuals ages 12-29 years following a booster dose exceeded the background rate but were lower compared to the rates following administration of the second primary series dose of Pfizer-BioNTech COVID-19 Vaccine.[181]

Finally, Petitioner asserts that "[t]he long-term effects of vaccine-induced myocarditis in this age group [are] unknown and, unfortunately, will only be learned with time and at the expense of those children who have suffered, but there is the potential that these cases could potentially

[178] Petition at 12.
[179] Patone, et al. Risk of Myocarditis Following Sequential COVID-19 Vaccinations by Age and Sex, medRxiv (Dec. 25, 2021), preprint: 2021.12.23.21268276, doi: https://doi.org/10.1101/2021.12.23.21268276.
[180] Id.
[181] Klein, N. Shimabukuro, T., CDC Advisory Committee on Immunization Practices, Updates on safety of COVID-19 booster dose (slide presentation), at 44, (Apr. 20, 2022), https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-04-20/03-COVID-Klein-Shimabukuro-508.pdf.

result in serious chronic conditions consistent with other forms of myocarditis."[182] FDA notes that information is not yet available about potential long-term sequelae and outcomes for individuals with post-mRNA vaccination myocarditis, and a mechanism of action by which the vaccine could cause myocarditis and pericarditis has not been established. Although, as noted above, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management,[183] FDA agrees that it is important to

[182] Petition at 15. In support of this statement, Petitioner cites a 2012 article published in *Heart Vessels* examining long-term outcomes of acute myocarditis in children. See Abe, et al., Clinical Characteristics and Long-Term Outcome of Acute Myocarditis in Children, Heart Vessels (2013), 28: 632–638, https://doi.org/10.1007/s00380-012-0296-8. The authors retrospectively studied 24 patients diagnosed with acute myocarditis (AM) and concluded that "[t]he long-term survival rate of children with AM was fair" but that "the outcome in most patients with reduced [left ventricular ejection fraction] after AM was poor." Id. This article predates by many years the emergence of the SARS-CoV-2 virus and thus, as Petitioner acknowledges, does not address experience with post-COVID-19 vaccination myocarditis; the article thus does not present new information that changes FDA's determination that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks for individuals 12-15 years of age. Petitioner goes on to cite five other publications for the proposition that "[n]umerous studies since have confirmed the seriousness of myocarditis." Petition at 15 n.77. FDA does not dispute that myocarditis can be serious and, as described elsewhere in this response has taken action to mitigate and monitor potential increased risk of myocarditis following vaccination with mRNA vaccines. However, the cited publications do not establish that cases of myocarditis following COVID-19 vaccination have been more serious than FDA has recognized. For example, Petitioner states that an article published in *Environmental Research and Public Health* found "persistent myocardium injury from COVID-19 vaccination after three months in all five members of teenage study group." Id. (citing Puchalski, et al., COVID-19-Vaccination-Induced Myocarditis in Teenagers: Case Series with Further Follow-Up, Int J Environ Res Public Health (Mar. 15, 2022), 19(6): 3456, doi:10.3390/ijerph19063456). While article states that "persistent myocardium injury features were detected in the whole [5-person] study group" and concludes that "complete resolution of the inflammatory process may last over 3 months[,]" it also notes that myocarditis associated with COVID-19 vaccines "seems to be a mild disease with fast clinical recovery[.]" Puchalski, et al., (2022). The article further notes that "[v]accination remains the most effective and safe COVID-19 weapon for adults and in the paediatric population." Id. Petitioner cites a study published in the *New England Journal of Medicine,* in which the authors describe a single fulminant fatal case but also conclude that "[t]he clinical presentation of myocarditis after vaccination was usually mild." Mevorach, et al., Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel, N Engl J Med (Dec. 2, 2021), 385: 2140-2149, doi:10.1056/NEJMoa2109730. Petitioner also cites a cases series of eight adolescents who presented with myopericarditis following vaccination with the Pfizer-BioNTech COVID-19 Vaccine, which reports that "[i]n 7 of the 8 patients, their symptoms were either self-limited or resolved after nonsteroidal anti-inflammatory medication." Tano, et al., Perimyocarditis in Adolescents After Pfizer-BioNTech COVID-19 Vaccine, J Pediatric Infect Dis Soc (Nov. 11, 2021), 10(10): 962-966, doi: 10.1093/jpids/piab060. Another case series cited by petitioner was of seven 14-19 year-old males with myocarditis or myopericarditis following COVID-19 vaccination. This case series reports that "[a]ll 7 patients resolved their symptoms rapidly. Three patients were treated with nonsteroidal anti-inflammatory drugs only, and 4 received intravenous immunoglobulin and corticosteroids." Marshall, et al., Symptomatic Acute Myocarditis in 7 Adolescents After Pfizer-BioNTech COVID-19 Vaccination, Pediatrics (Sept. 2021), 148(3): e2021052478, doi: 10.1542/peds.2021-052478. The final publication Petitioner cites is a report of 13 cases of identified myopericarditis in patients ranging from 12- to 17-years old following receipt of the Pfizer-BioNTech COVID-19 Vaccine. The report states that "[t]he median hospital length of stay was 2 days (range, 1-4 days) with no intensive care unit admission, significant morbidity, or mortality." Schauer, et al., Myopericarditis After the Pfizer Messenger Ribonucleic Acid Coronavirus Disease Vaccine in Adolescents, J Pediatr (Nov. 2021), 238: 317-320, doi: 10.1016/j.jpeds.2021.06.083. The cited articles also do not change our determination that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks for individuals 12-15 years of age.

[183] CDC, CDC Advisory Committee on Immunization Practices, Updates on safety of COVID-19 booster dose (slide presentation). April 20, 2022. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-04-20/03-COVID-Klein-Shimabukuro-508.pdf.; Oster, et al., Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US from December 2020 to August 2021, 2022.

monitor and gain a better understanding of long-term outcomes and factor new information into benefit-risk assessments. To help address these questions, the sponsor is conducting additional post-authorization studies to evaluate the association between Pfizer-BioNTech COVID-19 Vaccine and a pre-specified list of adverse events of special interest, including myocarditis and pericarditis.[184] Other efforts are also underway to gather more information. For example, CDC is conducting surveys of patients (or their parents or guardians) and healthcare providers to gather information about myocarditis after mRNA COVID-19 vaccination. CDC and FDA will use this information to guide recommendations on the safe use of COVID-19 vaccines.[185]

In sum, to the extent that the Petition asserts that the risk-benefit criterion for issuance of EUAs is no longer met on the basis of myocarditis and pericarditis risks, we disagree. While post-authorization data have identified increased risks of myocarditis and pericarditis, the Petition has not shown that these risks undermine FDA's 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 12-15 years of age.

Petitioner's Claims Regarding Other Potential Risks

Petitioner raises concerns about other purported known and potential risks, seemingly as part of the Petition's arguments about the Pfizer-BioNTech COVID-19 Vaccine not having a favorable benefit-risk relationship. According to the Petition, "an April 2022 study presented evidence that mRNA 'vaccination induces a profound impairment in type I interferon signaling, which has diverse adverse consequences to human health.'"[186] The "study" cited by Petitioner refers to a review article published in *Food and Chemical Toxicology* that "summarizes the current literature on mRNA and its effects on the molecular biology within human cells."[187] Petitioner quotes the authors' claim to "show evidence from the VAERS database supporting our hypothesis" that the COVID-19 mRNA vaccines can cause "potential profound disturbances in regulatory control of protein synthesis and cancer surveillance."[188] However, the article's discussion of VAERS reports does not provide such evidence.[189] The article does not provide

[184] We note that for Comirnaty, the sponsor is also required to conduct post-marketing requirement (PMR) studies to assess known serious risks of myocarditis and pericarditis as well as to identify an unexpected serious risk of subclinical myocarditis (these PMRs are described in Comirnaty BL 125742/0 approval letter dated August 23, 2021).

[185] CDC, COVID-19, Investigating Long-Term Effects of Myocarditis, https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes html (accessed June 8, 2022).

[186] Petition at 17.

[187] Seneff, et al., Innate Immune Suppression by SARS-CoV-2 mRNA Vaccinations: The Role of G-Quadruplexes, Exosomes, and MicroRNAs, Food & Chemical Tox. (Apr. 8, 2022), 164: 113008, https://doi.org/10.1016/j.fct.2022.113008.

[188] Petition at 17.

[189] For example, in support of a link between mRNA COVID-19 vaccines and neurodegenerative diseases, the authors note that "[d]ecreased mobility can be caused by Parkinson's disease, and there were a striking 8,975 cases [of decreased mobility] listed for 2021 and COVID-19 vaccines. Alzheimer's and Parkinson's are diseases that normally take decades to develop, and ordinarily one would assume that a vaccine has nothing to do with it." Seneff, et al., Innate Immune Suppression by SARS-CoV-2 mRNA Vaccinations: The Role of G-Quadruplexes, Exosomes, and MicroRNAs, 2022. Although the authors provide no information to indicate that they confirmed the VAERS reports of decreased mobility were associated with Parkinson's or another neurodegenerative disease, they suggest that this number of reports is evidence of their hypothetical link between those diseases and mRNA COVID-19 vaccines. Id. That is not the case.

new data or information regarding mRNA vaccines or impairment in type I interferon signaling that is of the scientific quality that FDA would consider in making regulatory decisions. Accordingly, the Petition does not provide evidence that mRNA COVID-19 vaccines "induce a profound impairment in type I interferon signaling" or that they present various other risks referenced in the Petition.

The Petition further asserts that additional "potential risks must also be taken into account." Petitioner states that "[v]accinating against rapidly evolving viruses increases the risk of original antigenic sin and antibody dependent enhancement. Some experts also fear that doing so will lead to highly infectious and highly virulent variants of SARS-CoV-2 that will be resistant to any spike-based COVID-19 vaccines."[190] In support of this proposition, the Petition points to a document posted online and blog post authored by Dr. Geert Vanden Bossche, as well as a video posted online that features him.[191] None of these materials appears to have been published in a scientific journal, nor do they present any new or original data. Rather, they present various theories and hypotheses[192] and thus, do not provide evidence that use of COVID-19 vaccines will "increase[] risk of original antigenic sin and antibody dependent enhancement" that is of the scientific quality FDA would consider in making regulatory decisions. Nor do they provide such evidence that COVID-19 vaccination will "lead to highly infectious and highly virulent variants of SARS-CoV-2 that will be resistant to any . . . COVID-19 vaccines" targeting the S protein.[193]

In addition, Petitioner claims that data from the United Kingdom "strongly suggest that the fully vaccinated have been suffering Antibody Dependent Enhancement . . . since at least the beginning of January 2022 and that COVID-19 death rates in vaccinated but unboosted individuals [were] higher than for those who had never been vaccinated.[194] The United Kingdom Office of National Statistics (ONS) data Petitioner references presents age-standardized mortality rates (ASMRs) for deaths involving COVID-19 by vaccination status between January 1, 2021 and March 31, 2022 in England; this report does not mention "antibody dependent enhancement."[195]

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[190] Petition at 17.
[191] Id. at 17-18.
[192] See, e.g., Vanden Bossche, Poor Virus-Neutralizing Capacity in Highly C-19 Vaccinated Populations Could Soon Lead to a Fulminant Spread of Sars-CoV-2 Super Variants that are Highly Infectious and Highly Virulent in Vaccinees While Being Fully Resistant to all Existing and Future Spike-Based C- 19 Vaccines, at 6 (March 2022), https://mcmillanresearch.com/wp-content/uploads/2022/03/GVBs-analysis-of-C-19-evolutionary-dynamics.pdf (describing the paper as a "theory [that] is now translating in very concerning predictions about the potential implications of the ongoing C-19 mass vaccination program on both, individual and public health.").
[193] Petition at 17. The Petition also cites an article published in the *Journal of Translational Autoimmunity* to support this proposition. We note that this article was published online by April 9, 2020. FDA has since authorized and licensed vaccines that meet the applicable statutory standards for safety and effectiveness, and the article does not account for the body of evidence regarding COVID-19 and the mRNA Vaccines subsequent to its publication. See, e.g., Lyons-Weiler, Pathogenic Priming Likely Contributes to Serious and Critical Illness and Mortality in COVID-19 via Autoimmunity, J. Translational Autoimmunity (Apr. 2020), 3: 100051, https://doi.org/10.1016/j.jtauto.2020.100051 ("[O]f course no vaccine against SARS-CoV-2 has yet been tested in animals and therefore we do not yet know if pathogenic priming is in fact expected.").
[194] Petition at 18.
[195] ONS, Deaths Involving COVID-19 by Vaccination Status, England: Deaths Occurring Between 1 January 2021 and 31 March 2022, (May 16, 2022), https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsinvolvingcovid19byvaccinationstatusengland/deathsoccurringbetween1january2021and31march2022.

Petitioner appears to reference Figure 1 of the ONS report, which presents monthly ASMR for all people (not broken down by age group). Figure 1 indicates that the ASMRs for deaths involving COVID-19 were higher for some vaccinated individuals than for those unvaccinated, while showing a lower ASMR for individuals that have received a third or booster dose compared to unvaccinated. However, the Petition ignores several key statements in the report regarding these data. For example, ONS states that these "age-adjusted rates are not equivalent to measures of vaccine effectiveness; they account for differences in age structure and population size, but there may be other differences between the groups (particularly underlying health) that affect mortality rates[.]"[196] The report also notes that "[c]hanges in non-COVID-19 mortality by vaccination status are largely driven by the changing composition of the vaccination status groups; this is because of the prioritisation of people who are clinically extremely vulnerable or have underlying health conditions, and differences in timing of vaccination among eligible people."[197] We agree with the ONS that these ASMR data are not equivalent to measures of vaccine effectiveness. These data do not demonstrate that "the fully vaccinated have been suffering Antibody Dependent Enhancement" as Petitioner argues.[198,199] We also note that recent CDC data on age-adjusted rates of COVID-19 deaths showed that in March 2022, unvaccinated people 12 years of age and older had 17 times higher COVID-19 associated death rates compared to those with primary series and booster dose.[200]

Thus, to the extent that the Petition asserts that the risk-benefit criterion for issuance of EUAs is no longer met on the basis of the concerns discussed in this section, we disagree. The Petition has not shown that these concerns undermine FDA's 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 12-15 years of age.

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[196] Id.

[197] Id.

[198] The Petition also cites a post to the website of HART, which calls for an investigation of a purported "increase in male mortality in 15-19 year olds" and speculates that a purported increase in the number of "excess deaths" among this age group between May 1 and September 17, 2021 in England and Wales may be tied to COVID-19 vaccination. Petition at 18. See Recent Deaths in Young People in England and Wales, HART (Oct. 11, 2021), https://www.hartgroup.org/recent-deaths-in-young-people-in-england-and-wales/. The post cites no data that identifies the cause of death for these individuals and does not demonstrate that fully vaccinated individuals in the United Kingdom are "suffering Antibody Dependent Enhancement." See id. ("Although there may be a number of explanations for these findings, further investigation of the cause of these deaths is warranted.")

[199] Petitioner cites a *New England Journal of Medicine* editorial as further support for the notion that the ONS report data suggest vaccinated individuals are suffering antibody dependent enhancement. Petition at 18. The editorial notes the "theoretical problem of an 'original antigenic sin'—a decreased ability to respond to a new immunogen because the immune system has locked onto the original immunogen." The editorial describes this as a "potential problem [that] could limit our ability to respond to a new variant." Id. It does not suggest that vaccinated individuals in the United Kingdom are dying at a higher rate than unvaccinated or that those vaccinated individuals are "suffering [a]ntibody [d]ependent [e]nhancement." See Offit, Covid-19 Boosters — Where from Here?, N Engl J Med (Apr. 28, 2022), 386: 1661-1662, https://www.nejm.org/doi/full/10.1056/NEJMe2203329.

[200] CDC, COVID-19 Epidemiology and Vaccination Rates in the United States, at 20, (June 7, 2022), available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-7-2022-meeting-announcement#event-materials.

Petitioner's Claims Regarding "Natural Immunity"

The Petition argues that "[f]urther diminishing the benefits of vaccination is the current rate of natural immunity in this population." The Petition appears to make arguments related to "natural immunity" to say that this "immunity" serves to "diminish[] the benefits of vaccination" such that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine do not outweigh the known and potential risks.[201] However, numerous immunologic studies and a growing number of epidemiologic studies have shown that vaccinating previously infected individuals significantly enhances their immune response and reduces the risk of subsequent infection, including in the setting of increased circulation of more infectious variants.[202]

The Petition's arguments regarding "natural immunity" do not undermine the benefit-risk analysis supporting FDA's authorization. The Petition points to a CDC report to show that "as of February 2022, approximately 75% of children ages 12-17 had seroprevalence of infection-induced SARS-CoV-2 antibodies" and states that "[c]urrent NIH data shows the percentage is even higher at 89.4% of children 0-17 as of February 2022."[203] Petitioner also cites several publications for the proposition that "[t]he superior protective effect of natural immunity is now beyond dispute."[204] However, the sources cited do not establish this proposition.[205] For example, the Petition states that "[a]ccording to the CDC's January 28, 2022 MMWR, unvaccinated individuals with prior COVID-19 infection had a lower rate of COVID-19-associated hospitalization than vaccinated individuals without a prior COVID-19 infection ."[206] In fact, the study found changing patterns across the study period.[207] In the pre-Delta period, the study found that hospitalization rates were higher among persons who survived a previous infection than persons who were vaccinated without a previous COVID-19 diagnosis; however, this pattern shifted as the Delta variant became predominant. During October 3-16, 2021, for example, compared with hospitalization rates among unvaccinated persons without a previous COVID-19 diagnosis, individuals who survived a previous infection had lower hospitalization rates than persons who were

[201] Petition at 13-14.
[202] CDC, Science Brief: SARS-CoV-2 Infection-induced and Vaccine-induced Immunity, (Oct. 29, 2021), https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/vaccine-induced-immunity html (accessed June 13, 2022).
[203] Petition at 13. We note that Petitioner theorizes that "the rate is almost certainly closer to 100% as more time has passed" but cites no data to support that figure.
[204] Id.
[205] See Gazit, et al., Persons With Naturally Acquired Immunity With and Without Subsequent Receipt of a Single Dose of BNT162b2 Vaccine, Annals of Internal Medicine (May 2022), https://doi.org/10.7326/M21-4130 (concluding that "[p]ersons previously infected with SARS-CoV-2 gained additional protection against reinfection and COVID-19 from a subsequent single dose of the BNT162b2 vaccine [but that] even without a subsequent vaccination, reinfection appeared relatively rare"); Flacco, et al., Risk of SARS-CoV-2 Reinfection 18 Months After Primary Infection: Population-Level Observational Study, Front. Public Health (May 2, 2022), https://www.frontiersin.org/article/10.3389/fpubh.2022.884121 ("[T]he incidence of reinfection did not vary substantially over time: after 18–22 months from the primary infection, the reinfection rate was still 6.7‰, suggesting that protection conferred by natural immunity may last beyond 12 months. The risk of reinfection was significantly higher among females, unvaccinated subjects, and during the Omicron wave.").
[206] Petition at 14.
[207] CDC, COVID-19 Cases and Hospitalizations by COVID-19 Vaccination Status and Previous COVID-19 Diagnosis — California and New York, May–November 2021, Morb Mortal Wkly Rep. (Jan. 19, 2022), 71(4): 125–131, https://www.cdc.gov/mmwr/volumes/71/wr/mm7104e1 htm.

vaccinated without a previous COVID-19 diagnosis. [208] The CDC noted that this analysis of data from New York and California ended prior to widespread implementation of booster doses.[209]

The Petition also cites a recent study finding that "'[f]or any given viral copy number, the odds of anti-N seropositivity were 13.67 times higher for the placebo arm than the control arm" and claims that this "confirm[s] vaccine-induced immunity is inferior to natural immunity, but it also demonstrates vaccine immunity appears to inhibit an individual's ability to acquire natural immunity to the nucleocapsid protein of the virus."[210] But that claim is not supported by the cited study.[211]

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.[212] 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.[213] The Petition does not demonstrate that "[t]he superior protective effect of natural immunity is now beyond dispute."

In addition, the Petition states that "prior COVID-19 infection . . . has been shown to increase the severity of side effects" and cites a publication in *The Lancet Infectious Diseases* for the proposition that "[s]ystemic side-effects were more common (… 2.9 times after the first dose of BNT162b2) among individuals with previous SARS-CoV-2 infection than among those without known past infection."[214] However, this publication does not support that prior COVID-19 infection "increase[s] the severity of [vaccine] side effects." The study assessed adverse effects of the Pfizer-BioNTech COVID-19 Vaccine and a vaccine manufactured by AstraZeneca (ChAdOx1 nCoV-19) in use in the United Kingdom and self-reported infection rates following

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[208] Id. ("During October 3–16, compared with hospitalization rates among unvaccinated persons without a previous COVID-19 diagnosis, hospitalization rates were 19.8-fold lower (95% CI = 18.2–21.4) among vaccinated persons without a previous COVID-19 diagnosis, 55.3-fold lower (95% CI = 27.3–83.3) among unvaccinated persons with a previous COVID-19 diagnosis, and 57.5-fold lower (95% CI = 29.2–85.8) among vaccinated persons with a previous COVID-19 diagnosis.")

[209] CDC, CDC Statement on MMWR: COVID-19 Cases and Hospitalizations by COVID-19 Vaccination Status and Previous COVID-19 Diagnosis — California and New York, May–November 2021 (Jan. 19, 2022), https://www.cdc.gov/media/releases/2022/s0120-covid-19-cases html.

[210] Petition at 13-14.

[211] Follman, 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. This article does not examine whether vaccine immunity is inferior to natural immunity. We note that in the Preprint, the study concludes "[a]s a marker of recent infection, [anti-nucleocapsid antibodies] may have lower sensitivity in [Moderna COVID-19 Vaccine]-vaccinated persons who become infected."

[212] 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.

[213] 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: http://dx.doi.org/10.15585/mmwr.mm7032e1external icon.

[214] Petition at 16.

vaccination.[215] The study found that "[i]ndividuals with evidence of past SARS-CoV-2 infection were . . . more likely to have adverse effects than those without evidence of past infection with both vaccines" but did not report an increased severity in adverse effects for those with past infection. Instead, the study reported that "short-term adverse effects of both vaccines are moderate in frequency, mild in severity, and short-lived" and noted observation of "substantially lower rates of severe and mild side-effects than observed in phase 3 trials."[216]

We note that history of infection prior to vaccination is not usually known in adverse event reports (either because it wasn't reported, or because it could have been asymptomatic and the patient never knew they had infection). Likewise, there could be a reporting bias for a reporting system like VAERS, which relies on vaccine recipients, healthcare providers, or others to initiate reports to the system, because individuals who were infected previously might be more likely to report adverse events. However, FDA, together with CDC, has not become aware of data from VAERS to suggest an increased frequency of adverse events in vaccine recipients who were infected with SARS-CoV-2 prior to vaccination. FDA and CDC Medical Officers conduct ongoing review of certain, serious adverse events of special interest for the COVID vaccines. These reviews often include examination of the narrative and other fields which could contain information about past infection, if provided. Additionally, CDC and the VAERS Program contractor collect follow-up medical records for certain serious reports. Teams of physicians, nurses, and other reviewers abstract key clinical details, including medical history, from these records. The reviewers conducting these on-going surveillance efforts have not identified patterns of adverse events associated with prior infection.

In summary, the Petition does not present any information regarding "natural immunity" that changes FDA's determination that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, when used to prevent COVID-19 in individuals 12-15 years of age, outweighs its known and potential risks.

e. Conclusion Regarding Section 564(c)(2) of the FD&C Act

In sum, FDA carefully considered the evidence regarding the known and potential benefits and risks of the Pfizer-BioNTech COVID-19 Vaccine when it authorized its use for individuals 12-15 years of age on May 10, 2021 and has carefully monitored post-authorization evidence regarding those benefits and risks. The Petition does not present any information that warrants a reversal in FDA's determination that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine, when used to prevent COVID-19 in individuals 12-15 years of age, outweighs its known and potential risks. Therefore, the criterion under section 564(c)(2) of the FD&C Act continues to be met.

[215] Menni, et al., Vaccine Side-Effects And SARS-Cov-2 Infection After Vaccination In Users Of The COVID Symptom Study App In The UK: A Prospective Observational Study, The Lancet Infectious Diseases (Jul. 1, 2021), 21(7): 939-949, doi:10.1016/S1473-3099(21)00224-3.
[216] Id.

4. No Alternatives

Section 564(c)(3) of the FD&C Act provides one of the required statutory factors that must be met in order for a product to be granted an EUA. This statutory provision requires that "there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating [the serious or life-threatening disease or condition]." The Petition does not argue for revocation of the EUA for the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 12-15 years of age on the grounds that there is an adequate, approved, and available alternative preventing 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 16 years of age and older. Spikevax is approved for the prevention of COVID-19 in individuals 18 years of age or older.

Therefore, there are no adequate, approved, and available alternatives to the Pfizer-BioNTech COVID-19 Vaccine for individuals 12-15 years of age. The criterion under section 564(c)(3) of the FD&C Act is met.

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

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

> significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.[217]

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 12-15 years

[217] EUA Guidance at 29.

of age appropriate to protect the public health or safety. As stated previously in this response, FDA determined the EUA standard is met for the Pfizer-BioNTech COVID-19 Vaccine in such individuals because data submitted by the sponsors demonstrated in a clear and compelling manner that the known and potential benefits of this vaccine, when used to prevent COVID-19, outweigh the known and potential risks in individuals 12 through 15 years of age, and that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating COVID-19 in this population.

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 COVID-19 Vaccine, to support a revocation of the Pfizer-BioNTech COVID-19 Vaccine EUA for use in individuals 12-15 years of age. As described above, the Petition has not provided information demonstrating that that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine in individual 12-15 years of age population are outweighed by the known and potential risks of the product. 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 12-15 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 12-15 years of age. Accordingly, as noted above, we deny Petitioner's request that FDA "revoke the May 10, 2021 reissuance of the EUA for the use of Pfizer-BioNTech's COVID-19 [V]accine for children ages 12 through 15."

B. Petitioner's Request that FDA Refrain from Authorizing Moderna COVID-19 Vaccine for Emergency Use in Individuals Ages 12 through 17

In this section, we address Petitioner's request that "FDA refrain from authorizing Moderna's current COVID-19 vaccine for children ages 12 through 17." In support of this request, the Petition states that "[f]or the reasons set forth above, Moderna's current vaccine presents a far greater risk than benefit to 12- to 17-year-olds, particularly where Moderna's vaccine presents an even higher risk profile to this age group than Pfizer's vaccine."[218] We interpret the reference to "the reasons set forth above" to mean Petitioner's arguments in support of its request to revoke the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 12-15 years of age. Therefore, to the extent such arguments apply to the Moderna COVID-19 Vaccine for use in individuals 12-17 years of age, we incorporate our above responses to those arguments in this section. Otherwise, we address below only the specific arguments that Petitioner raises with respect to Moderna COVID-19 Vaccine for use in that population.

i. EUA for 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, the EUA was amended to authorize the use of the Moderna COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-

[218] Petition at 3, 18.

CoV-2 in individuals 6 months through 17 years of age.[219] Currently, the Moderna COVID-19 Vaccine[220] 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

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,[221] and the data upon which it was based, in detail. [222]

[219] 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. This Letter of Authorization will be posted on www.fda.gov.
[220] 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.
[221] 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.
[222] 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.

ii. The Standard for Issuance of an EUA Is Met

As described above, based on the February 4, 2020, determination made by the Secretary of HHS pursuant to section 564(b)(1)(C) of the FD&C Act[223] and the Secretary's COVID-19 EUA Declaration, FDA may issue an EUA during the COVID-19 pandemic after FDA concludes that certain statutory criteria are met. On June 17, 2022, FDA authorized 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 after determining that the each of the statutory requirements in section 564 of the FD&C Act were met, as detailed in FDA's decision memorandum. Below we briefly address each criterion and any arguments the Petition makes regarding that criterion.

1. Serious or Life-Threatening Disease or Condition

For the reasons described above in section III.A.iv.1, FDA has concluded that SARS-CoV-2 can cause a serious or life-threatening disease or condition, including in individuals 12-17 years of age. Thus, the criterion in section 564(c)(1) of the FD&C Act is satisfied. With respect to its request that FDA refrain from authorizing the Moderna COVID-19 Vaccine for use in individuals 12-17 years of age, Petitioner states that "[b]ecause there is no health emergency for children, the FDA likewise lacks the legal authority to issue an EUA for Moderna's vaccine for 12- to 17-year-old children." To the extent this constitutes and argument that the criterion in section 564(c)(1) of the FD&C Act is not met, the Petitioner has not demonstrated that to be the case for the reasons described in section III.A.iv.1.

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. Vaccine effectiveness for the 12-17 years of age group was inferred by immunobridging, based on a comparison of immunogenicity endpoints, to a young adult age group (18-25 years of age) for whom vaccine effectiveness had been demonstrated in a Phase 3 efficacy trial. Additionally, descriptive efficacy analyses provided vaccine effectiveness estimates that are consistent with estimates from observational studies in adults from the corresponding time periods, supporting robust effectiveness against COVID-19 caused by the ancestral strain, Alpha, and Delta variants and more modest effectiveness against COVID-19 caused by the Omicron variant (corresponding to lower neutralizing antibody titers against Omicron as compared to the ancestral strain).[224]

With respect to its request that FDA refrain from authorizing the Moderna COVID-19 Vaccine for use in individuals 12-17 years of age, Petitioner does not state that the vaccine fails to meet the effectiveness criterion under section 564(c)(2)(A) of the FD&C Act. To the extent the

[223] 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.
[224] FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (June 16, 2022). This decision memorandum will be posted on www fda.gov.

Petition's arguments regarding immunobridging with respect to authorization of the Pfizer-BioNTech COVID-19 Vaccine are applicable to authorization of the Moderna COVID-19 Vaccine in this age group, we note that, for the reasons described in section III.A.iv.2, Petitioner fails to establish that the criterion in section 564(c)(2)(A) of the FD&C Act is not met. 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 may be effective to prevent, diagnose, or treat COVID-19 in the 12 through 17 years of age population. The basis for this determination is explained in detail in FDA's decision memorandum.

3. Benefit-Risk Analysis

Section 564(c)(2)(B) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude "the known and potential benefits of the product, when used to diagnose, prevent, or treat [the identified serious or life-threatening disease or condition], outweigh the known and potential risks of the product . . . ." Petitioner asserts that the "known benefits of Moderna's current COVID-19 vaccine for 12- to 17-year old do not outweigh the known and potential risks" citing concerns related to the size of Moderna's clinical trial and risks of myocarditis.

a. Petitioner's Claims Regarding Adequacy of Clinical Trial

Petitioner argues that, "[l]ike Pfizer's, Moderna's clinical trial was similarly underpowered. It included only 3,732 participants, only half of whom received the vaccine."[225] As an initial matter, the numbers Petitioner cites are incorrect. Moderna's EUA amendment request included safety and effectiveness data from two ongoing Phase 2/3 randomized, double-blinded and placebo-controlled trials 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, including 10,285 participants who received at least one dose of Moderna COVID-19 Vaccine. Among 3,726 participants 12-17 years of age, 2,486 received the Moderna COVID-19 Vaccine (100 µg dose) and 1,240 received saline placebo. The median follow-up duration in this adolescent age cohort for Moderna COVID-19 Vaccine recipients was 53 days post-Dose 2 for blinded, placebo-controlled follow-up and 312 days post-Dose 2 including unblinded follow-up. Regarding the claim that "like Pfizer's trial" Moderna's clinical trial was "underpowered" and to the extent the Petition argues that the trials supporting authorization of the Moderna COVID-19 Vaccine for use in individuals 12-17 years of age were insufficient in size, the Petition does not demonstrate this to be the case for the reasons described in section III.A.iv.3 and the reasons describing FDA's authorization decision in FDA's decision memorandum.[226]

FDA authorized the Moderna COVID-19 Vaccine for emergency use for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12-17 years of age after reaching a

[225] Petition at 19.

[226] FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (June 16, 2022). This decision memorandum will be posted on www fda.gov.

determination that, among other things, the known and potential benefits of the vaccine, when used to prevent COVID-19 in this population, outweigh its known and potential risks.[227]

b. Petitioner's Claims Regarding Risk of Myocarditis

Apparently to suggest that the known risks of the Moderna COVID-19 Vaccine outweigh the known benefits of the vaccine, Petitioner argues that "[t]he risks of the Moderna vaccine to [individuals 12-17 years of age] are even more significant than those of the Pfizer vaccine."[228] To support this argument, Petitioner cites to one study of "23 million Nordic residents," claiming that this study "confirmed that mRNA shots sharply raised the risk of heart damage in those who received them last year and Moderna's vaccine was significantly more dangerous particularly for young men."[229] The study at issue concluded that "the risk of myocarditis … was more pronounced after the second dose of [Moderna COVID-19 Vaccine] than after the second dose of [Pfizer-BioNTech COVID-19 Vaccine], and the risk was highest among males aged 16 to 24 years."[230] Petitioner also references a March 2021 statement from the European Medical Association (EMA)[231] that provides a high-level summary of French and Nordic studies that found a higher number of "extra cases of myocarditis" in certain male populations for Spikevax than for Comirnaty, along with an October 2021 statement from the Public Health Agency of Canada that "[v]accine safety surveillance data in Canada also suggest relatively higher rates of myocarditis and/or pericarditis reported after Spikevax (Moderna) vaccination compared to Comirnaty (Pfizer-BioNTech)."[232,233] Aside from the Nordic study, the Petition provides no other data to support the claim that "[t]he risks of the Moderna vaccine to [individuals 12-17 years of age] are even more significant than those of the Pfizer vaccine."

In contrast, FDA has considered many different data sources, including the Nordic study referenced by Petitioner, to understand the potential increased risk of myocarditis/pericarditis associated with the mRNA vaccines, including any differences between the Pfizer-BioNTech COVID-19 Vaccine and Moderna COVID-19 Vaccine. In spring and summer 2021, after

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[227] For an extensive discussion of FDA's analysis of the clinical trial data regarding the risks and benefits of the Pfizer-BioNTech COVID-19 Vaccine, see FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda.

[228] Petition at 19.

[229] Id.

[230] Karlstad, et al., SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents, JAMA Cardiology (Apr. 20, 2022), 7(6): 600-612, doi: 10.1001/jamacardio.2022.0583.

[231] EMA, Meeting Highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 29 November – 2 December 2021, (Mar. 12, 2021), https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-29-november-2-december-2021.

[232] Public Health Agency of Canada, Statement from the Council of Chief Medical Officers of Health (CCMOH): Update on COVID-19 Vaccines and the Risk of Myocarditis and Pericarditis (Oct. 1, 2021), https://www.canada.ca/en/public-health/news/2021/10/statement-from-the-council-of-chief-medical-officers-of-health-ccmoh-update-on-covid-19-vaccines-and-the-risk-of-myocarditis-and-pericarditis.html. This statement noted that "the available data indicate that the majority of affected individuals, even if hospitalized, experience relatively mild illness, respond well to conservative treatment, and recover quickly." Id.

[233] The Petition also notes that some other countries "have ceased administering or recommended against the use of Moderna's vaccine in young adults and/or young adult males." Petition at 19. 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.

Moderna's submission of the EUA amendment requesting use of a two-dose series of the vaccine in adolescents 12-17 years of age, a number of published reports suggested there was a potential increased risk of myocarditis/pericarditis in young males following vaccination with the second dose of either the Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine.[234] By the fall of 2021, FDA reviewed results from seven surveillance systems which suggested an estimated two- to seven-fold increased risk of myocarditis/pericarditis following Moderna COVID-19 Vaccine vaccination as compared to Pfizer-BioNTech COVID-19 Vaccine in passive surveillance systems in multiple European countries and Canada. An active surveillance study conducted by CDC's VSD, employing a direct head-to-head comparison of Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine indicated that myocarditis/pericarditis rates following vaccination with Moderna COVID-19 Vaccine were more than two times higher than with Pfizer-BioNTech COVID-19 Vaccine after Dose 2 in young males (relative risk [RR]: 2.26, 95% CI: 1.09, 4.63).[235] Although there are significant limitations in results generated by these comparisons, the reported differences in myocarditis/pericarditis risk between the two mRNA vaccines across multiple data sources were concerning.

Results from subsequent analyses conducted by the CDC and FDA in the fall of 2021 indicated only a small difference in myocarditis/pericarditis risk between Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine. A comparison using the BEST system reported a smaller 20% increase in myocarditis/pericarditis rates among Moderna COVID-19 Vaccine recipients as compared to Pfizer-BioNTech COVID-19 Vaccine recipients, a finding that was not statistically significant (RR: 1.21, 95% CI: 0.56, 2.60).[236] At the time, the preponderance of evidence continued to indicate a higher magnitude of myocarditis/pericarditis risk following vaccination with the second dose of Moderna COVID-19 Vaccine as compared to Pfizer-BioNTech COVID-19 Vaccine in young males.

As of May 2022, more data and cases of myocarditis/pericarditis following mRNA vaccination accumulated in surveillance systems globally and in the United States. Head-to-head comparisons from the Canadian and Ontario-Canada enhanced passive surveillance systems

[234] Montgomery, et al., Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military, JAMA Cardiol. (Jun. 29, 2021), 6(10): 1202-1206, doi:10.1001/jamacardio.2021.2833; Rosner, et al., Myocarditis Temporally Associated with COVID-19 Vaccination, Circulation (Jun. 2021), 144: 502–505, https://doi.org/10.1161/CIRCULATIONAHA.121.055891; Kim, et al., Patients with Acute Myocarditis Following mRNA COVID-19 Vaccination, JAMA Cardiol. (Jun. 2021), 6(10): 1196-1201, doi:10.1001/jamacardio.2021.2828; Marshall, et al., Symptomatic Acute Myocarditis in 7 Adolescents After Pfizer-BioNTech COVID-19 Vaccination, Pediatrics, 2021.; Diaz, et al., Myocarditis and pericarditis After Vaccination for COVID-19, JAMA (Aug. 4, 2021), 326(12): 1210-1212, doi:10.1001/jama.2021.13443; Klein, et al., Surveillance for Adverse Events After COVID-19 mRNA Vaccination, JAMA (Sept. 3, 2021), 326(14): 1390-1399, doi:10.1001/jama.2021.15072.

[235] CDC, COVID-19 vaccine safety updates. Advisory Committee on Immunization Practices (ACIP) October 21, 2021 meeting presentation, 2021, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf .

[236] See FDA, Vaccines and Related Biological Products Advisory Committee October 14–15, 2021 meeting presentation, Surveillance Updates of Myocarditis/Pericarditis and mRNA COVID-19 Vaccination in the FDA BEST System (2021), https://www fda.gov/media/153090/download.

indicated an approximately five-fold[237] to seven-fold for young males[238] increased risk for Moderna COVID-19 Vaccine compared to Pfizer-BioNTech COVID-19 Vaccine. International observational studies conducted in the United Kingdom,[239] Denmark,[240] Nordic countries,[241] Italy,[242] and France[243] suggested a three- to seven-fold differential risk for the Moderna COVID-19 Vaccine relative to the Pfizer-BioNTech COVID-19 Vaccine after Dose 2.

As of May of 2022, more robust results from new analyses run in U.S. surveillance systems show slight decreases in the risk differential between mRNA vaccines. Comparisons in VAERS indicated that there could be a smaller difference in risk between the Moderna and Pfizer COVID-19 Vaccines than previously identified in VAERS surveillance.[244] The most recent direct comparisons from both the CDC VSD and FDA BEST reported a non-statistically significant increase of 50% (RR =1.50, 95% CI: 0.86-2.61)[245] and 25% (RR =1.25, 95% CI: 0.80-1.94),[246] respectively, following vaccination of young males with Dose 2 of Moderna COVID-19 Vaccine compared with Pfizer-BioNTech COVID-19 Vaccine. Additionally, accrued data from CDC and other sources on myocarditis outcomes continued to strengthen the evidence that most cases of mRNA vaccine-associated myocarditis, including in pediatric age groups, are characterized by resolution of symptoms following conservative management, with no impact on quality of life reported by most patients who were contacted for follow-up at 90 days or more after reporting vaccine-associated myocarditis.[247]

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[237] Abraham, et al., Myocarditis and/or Pericarditis Risk After mRNA COVID-19 Vaccination: A Canadian Head-to-Head Comparison of BNT162b2 and mRNA-1273 Vaccines, Vaccine (May 25, 2022), preproof, https://www.sciencedirect.com/science/article/pii/S0264410X22006673 (accessed June 1, 2022).
[238] Buchan, et al. Epidemiology of Myocarditis and Pericarditis Following mRNA Vaccines in Ontario, Canada: By Vaccine Product, Schedule and Interval, medRxiv (Dec. 5, 2021), preprint: 2021.12.02.21267156, doi: https://doi.org/10.1101/2021.12.02.21267156.
[239] Patone, et al., Risk of Myocarditis Following Sequential COVID-19 Vaccinations by Age and Sex, 2021.
[240] Husby, et al., SARS-CoV-2 Vaccination and Myocarditis or Myopericarditis: Population Based Cohort Study, BMJ (Dec. 16, 2021), 375:e068665, doi: https://doi.org/10.1136/bmj-2021-068665.
[241] Karlstad, et al., SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents, 2022.
[242] Massari, et al., Post-Marketing Active Surveillance of Myocarditis and Pericarditis Following Vaccination With COVID-19 mRNA Vaccines in Persons Aged 12-39 Years in Italy: A Multi-Database, Self-Controlled Case Series Study, medRxiv (Feb. 8, 2022), preprint: 2022.02.07.22270020; doi: https://doi.org/10.1101/2022.02.07.22270020.
[243] EMA, Pharmacovigilance Risk Assessment Committee (PRAC), Signal assessment report on myocarditis and pericarditis with Spikevax - COVID-19 mRNA vaccine (nucleoside-modified) (French case-control study mentioned on pages 17-19), available at: https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-myocarditis-pericarditis-spikevax-previously-covid-19-vaccine-moderna-covid_en.pdf .
[244] Oster, et al., Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US from December 2020 to August 2021, JAMA (2022) 327(4):331–340. doi:10.1001/jama.2021.24110.
[245] Klein, Myocarditis Analyses in the Vaccine Safety Datalink: Rapid Cycle Analyses and "Head-to-Head" Product Comparisons, Feb 4, 2022, available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/10-COVID-Klein-508.pdf .
[246] Wong, et al., Risk of Myocarditis and Pericarditis after the COVID-19 mRNA Vaccination in the USA: A Cohort Study in Claims Databases, Lancet (Jun. 11, 2022), 399(10342): 2191-2199, https://doi.org/10.1016/S0140-6736(22)00791-7.
[247] Oster, et al., Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021, 2022; CDC, Vaccines and Related Biological Products Advisory Committee, Update on myocarditis following mRNA COVID-19 vaccination, at slide 12-14 (June 14, 2022), https://www.fda.gov/media/159228/download.

In conclusion, several international passive and active surveillance data sources suggest a higher myocarditis/pericarditis risk Moderna COVID-19 Vaccine relative to Pfizer-BioNTech COVID-19 Vaccine. However, these data have limitations and uncertainties, especially for passive surveillance sources as compared to active surveillance results. More recent results from April and May 2022 analyses from three US surveillance systems do not support a difference in myocarditis/pericarditis risk for Moderna COVID-19 Vaccine as compared to Pfizer-BioNTech COVID-19 Vaccine or suggest a small difference because of uncertainties and broad confidence intervals.[248] Based on the totality of the available scientific evidence, the evidence regarding myocarditis/pericarditis risk does not create an unfavorable benefit-risk profile for use of the Moderna COVID-19 Vaccine to prevent COVID-19 in individuals 12-17 years of age. The Petition has not shown otherwise. FDA has determined that known and potential benefits of the Moderna COVID-19 Vaccine outweigh its known and potential risks for use in individuals 12-17 years old. The criterion under section 564(c)(2)(B) of the FD&C Act is satisfied.

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 that FDA should refrain from authorizing Moderna COVID-19 Vaccine for use in individuals 12-17 years of age on the grounds that there is an adequate, approved, and available alternative preventing 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 16 years of age and older. Spikevax is approved for the prevention of COVID-19 in individuals 18 years of age or older.

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 16 and 17 year-olds, and the Petition requests that FDA not authorize the Moderna COVID-19 Vaccine 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 16 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 12-17 years of age. The criterion under section 564(c)(3) of the FD&C Act is met.

[248] Oster, et al., Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021, JAMA (Jan. 2022); Klein, Myocarditis Analyses in the Vaccine Safety Datalink: Rapid Cycle Analyses and "Head-to-Head" Product Comparisons, Feb 4, 2022, available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/10-COVID-Klein-508.pdf; Wong, et al., Risk of Myocarditis and Pericarditis after the COVID-19 mRNA Vaccination in the USA: A Cohort Study in Claims Databases, Lancet (Jun. 11, 2022), 399(10342): 2191-2199, https://doi.org/10.1016/S0140-6736(22)00791-7.

5. Conclusion

For the reasons described above, FDA is denying your request to "refrain from authorizing Moderna's current COVID-19 vaccine for children ages 12 through 17."[249]

C. Petitioner's Request that FDA Require T-cell Assessment from COVID-19 Vaccine Developers as a Measure of Evaluating Vaccine Efficacy

Petitioner requests FDA to require "T-cell assessment from COVID-19 vaccine developers as a measure of evaluating vaccine efficacy."[250] We interpret this to be a request that FDA require sponsors of clinical investigations of vaccines for prevention of COVID-19 to include in those investigations "T-cell assessment as a measure of evaluating vaccine efficacy."[251] In support of this request, Petitioner attaches a letter sent to FDA from the authors of a recent article in *Science Immunology* asking that the Agency "include in its guidance to vaccine developers a recommendation for T-cell assessment in COVID-19 vaccine clinical trials to more comprehensively measure immune response."[252]

As noted in FDA's guidance on development of vaccines to prevent COVID-19, understanding of SARS-CoV-2 immunology, and specifically vaccine immune responses that might predict protection against COVID-19, is currently limited and evolving.[253] The *Science Immunology* article acknowledges this, stating that " a comprehensive understanding of the adaptive immune response to SARS-CoV-2 infection is imperative."[254] The article also notes that "[d]efining what constitutes a protective versus harmful T cell response [to SARS-CoV-2] warrants further investigation."[255] While FDA agrees that greater understanding of the role of T-cell response in protection against COVID-19 could be useful to the scientific and public health community, Petitioner has not provided information showing that T-cell assessment would provide meaningful information regarding efficacy for purposes of FDA's authorization or licensure of a vaccine to prevent COVID-19. FDA therefore denies the request to require sponsors to include such assessments in clinical investigations of vaccines for prevention of COVID-19.

D. Petition for Stay of Action

As noted above, we interpret the Petition to be a submission pursuant to 21 CFR 10.30 because Petitioner's requests do not ask FDA to stay the effective date of any administrative action; the Petition is also described as a "Citizen Petition" and follows the format prescribed in 21 CFR 10.30, rather than 10.35. However, to the extent your request that FDA refrain "from authorizing Moderna's current COVID-19 vaccine for children ages 12 through 17" could be construed as

[249] Petition at 3.
[250] Id.
[251] Sponsors are responsible for creating study designs. FDA reviews INDs and may place INDs on clinical holds pursuant to 21 CFR 312.42 if the Agency identifies certain deficiencies.
[252] Petition, Attachment 2 (Sources Part 2), at 115.
[253] Vaccine Development and Licensure Guidance at 9.
[254] Vardhana, et al., Understanding T-cell Responses to COVID-19 is Essential for Informing Public Health Strategies, Science Immunology (Mar. 24, 2022), 7(71), doi:10.1126/sciimmunol.abo1303.
[255] Id.

request for a stay of action, the Petition does not establish that the criteria for granting a stay are met.

i. Criteria for Granting an Administrative Stay of Action

FDA's regulation at 21 CFR 10.35(e) sets out the standard for review of a petition for stay of action (PSA) as follows, in part:

> The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition. The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:
>
> (1) The petitioner will otherwise suffer irreparable injury.
>
> (2) The petitioner's case is not frivolous and is being pursued in good faith.
>
> (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
>
> (4) The delay resulting from the stay is not outweighted by public health or other public interests.

As stated in the regulation, the Commissioner shall grant a stay if all four of the criteria in 21 CFR 10.35(e) apply. As explained below, we find that Petitioner has failed to demonstrate three of the four criteria in section 10.35(e). Consequently, we need not address whether Petitioner's request is not frivolous and is being pursued in good faith.

FDA also has the discretion to grant a stay if it is in the public interest and in the interest of justice to do so. We decline to grant a discretionary stay of action on that basis because Petitioner has not established that a stay would be in the public interest or the interest of justice. For the reasons described below, we believe that staying authorization of the Moderna COVID-19 Vaccine for use in individuals 12-17 years of age is not in the public interest, and Petitioner makes no showing as to why a stay would be in the interest of justice.

ii. Petitioner Has Not Demonstrated that All Four Criteria in 21 CFR 10.35(e) apply.

The Petition makes no showing that authorizing the Moderna COVID-19 Vaccine for use in individuals 12-17 years of age will cause Petitioner to suffer irreparable injury, nor does it address or demonstrate sound public policy grounds to support a stay.

To the extent the Petitioner's arguments that the known and potential risks of the Moderna COVID-19 Vaccine outweigh the known and potential benefits could be construed as an argument that the delay from staying authorization of the vaccine for use in 12-17 year-olds is not outweighed by public health or other public interests, we disagree. As is the case with all licensed or authorized vaccines, the Moderna COVID-19 Vaccine is being authorized for use in

individuals 12-17 years of age based on FDA's science-based decision-making process to assure our standards for safety and effectiveness are met.[256]

The public health and public interest in access to COVID-19 vaccines is strong. We conclude that staying authorization of the Moderna COVID-19 Vaccine for use in individuals 12-17 years of age during the current pandemic would not be in the public health or other public interest, and Petitioner has not demonstrated inadequacies in the clinical data supporting the EUA amendment request that undercut FDA's decision to authorize the vaccine, nor has Petitioner demonstrated that the known and potential risks of the Moderna COVID-19 Vaccine outweigh its known and potential benefits in this age group

For the foregoing reasons, to the extent the Petition could be construed as a PSA under 21 CFR 10.35, the PSA is denied.

IV. CONCLUSION

FDA has considered Petitioner's requests to revoke the EUA for use of the Pfizer-BioNTech COVID-19 Vaccine in children ages 12 through 15; refrain from authorizing the Moderna COVID-19 Vaccine for use in children ages 12 through 17; and require T-cell assessment from COVID-19 vaccine developers as a measure of evaluating vaccine efficacy. For the reasons given in this letter, FDA denies the requests and therefore denies the Petition in its entirety.

Sincerely,

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

cc: Dockets Management Staff

[256] For a vaccine with an EUA, those standards are described in section II.C. of this response.