October 11, 2022

Aaron Siri
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Re: Citizen Petition (Docket Number FDA-2022-P-1399)

Sent via email to: aaron@sirillp.com

Dear Mr. Siri,

This letter responds to the citizen petition you submitted June 29, 2022, 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 June 17, 2022 reissuance of the EUA letter of authorization for the use of Pfizer-BioNTech's COVID-19 vaccine for children ages 5 through 11 be revoked pursuant to 21 U.S.C. § 360bbb-3(g)";
2. "the June 17, 2022 reissuance of the EUA letter of authorization for use of Moderna's COVID-19 vaccine in children ages 6 through 11 be provoked [sic] pursuant to 21 U.S.C. § 360bbb-3(g)"; 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. We have carefully reviewed the Petition and other information available to the Agency. Based on our review of these materials, and for the reasons described below, we conclude that the Petition does not contain facts demonstrating any reasonable grounds for the requested actions. In accordance with Title 21 CFR (Code of Federal Regulations) 10.30(e)(3), and for the reasons stated below, FDA is denying the Petition.

[1] Petition at 3.

We note that Petitioner makes very similar arguments in the Petition to support its requests as Petitioner made in a citizen petition dated May 20, 2022[2] ("May 2022 Petition"). As discussed below, we will incorporate by reference our response to similar arguments in the May 2022 Petition Response issued June 17, 2022 ("May 2022 Response") where appropriate.

Here is an outline of our response:

[2] Docket No. 2022-P-0872-0001.

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 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. FDA has issued EUAs for vaccines to prevent COVID-19, including monovalent vaccines sponsored by Pfizer Inc. (Pfizer)[7] and ModernaTX, Inc. (Moderna)[8] that are the subject of this Petition. 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 12 years of age and older. On January 31, 2022, the Agency approved the BLA for Spikevax (COVID-19 Vaccine, mRNA), and the approval was granted to Moderna. Spikevax is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

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[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.
[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.

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] For additional background on the investigational new drug process, see the May 2022 Response at 3-5, which we incorporate by reference.

B. Licensed Vaccines Are Safe, Pure, and Potent

FDA has a stringent regulatory process for licensing vaccines.[11, 12] 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."[13] 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. For additional background on licensed vaccines, see the May 2022 Response at 5-6, which we incorporate by reference.

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

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[10] See 21 CFR 312.2(a) (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).
[11] 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.
[12] Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[13] Section 351(a)(2)(C)(i)(I) of the PHS Act.

virus that causes COVID-19.[14] 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.[15]

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.

For additional background on EUAs for COVID-19 vaccines, please see the May 2022 Response at 6-8, which we incorporate by reference.

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

[14] 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.
[15] COVID-19 EUA Declaration.

- 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.[16]

III. DISCUSSION

A. Petitioner's Request that FDA Revoke the June 17, 2022 Emergency Use Authorization for the Use of the Pfizer-BioNTech COVID-19 Vaccine in Individuals Ages 5 through 11 years

In this section, we address Petitioner's request that "the June 17, 2022 reissuance of the EUA letter of authorization for the use of Pfizer-BioNTech's COVID-19 vaccine for children ages 5 through 11 years be revoked pursuant to 21 U.S.C. § 360bbb-3(g)[.]"[17, 18]

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 October 29, 2021, when FDA authorized the emergency use of the Pfizer-BioNTech COVID-19 vaccine for the prevention of COVID-19 in individuals 5-11 years of age.[19] Currently, the Pfizer-BioNTech COVID-19 Vaccine[20] 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,

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[16] 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).

[17] Petition at 3.

[18] We note that the Petition discusses several assertions made or actions taken by CDC. For requests intended for CDC, you should contact CDC directly.

[19] For a description of all revisions to the EUA for Pfizer-BioNTech COVID-19 vaccine, see Pfizer-BioNTech COVID-19 Vaccine Letter of Authorization, August 31, 2022. This Letter of Authorization is posted on www.fda.gov.

[20] 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 monovalent 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.

- 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,
- Three-dose primary series for individuals 6 months through 4 years of age.

On August 31, 2022, the EUA was amended to authorize the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for the prevention of COVID-19 in individuals 12 years of age and older as a single booster dose administered at least 2 months after either:

- completion of primary vaccination with any FDA authorized or approved monovalent[21] COVID-19 vaccine, or
- receipt of the most recent booster dose with any FDA authorized or approved monovalent COVID-19 vaccine.

Petitioner specifically requests that FDA revoke the "June 17, 2022 reissuance of the EUA letter of authorization for the use of Pfizer-BioNTech's COVID-19 vaccine for children ages 5 through 11[.]"[22] We interpret the Petition to request revocation of the EUA for the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 5-11 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,[23] which discuss this determination, and the data upon which it was based, in detail.[24]

ii. The Standard for Revocation of EUAs Is Not Met

Petitioner argues that the June 17, 2022 "[g]ranting of the EUA for Pfizer's [v]accine for 5- to 11-[y]ear-[o]lds [w]as [u]nlawful" 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 5- to 11-year-olds was deficient," and (3) "[t]he alleged benefits of Pfizer's vaccine

[21] For purposes of this response, monovalent refers to any FDA authorized or approved COVID-19 Vaccine that contains or encodes the spike protein of only the Original SARS-CoV-2. These vaccines are: Pfizer-BioNTech COVID-19 Vaccine, COMIRNATY (COVID-19 Vaccine, mRNA), SPIKEVAX (COVID-19 Vaccine, mRNA), Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, and Novavax COVID-19 Vaccine, Adjuvanted.
[22] Petition at 3.
[23] 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; June 16, 2022; and August 31, 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.
[24] 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.

for 5- to 11-year-olds are heavily outweighed by the known and potential risks."[25] Petitioner has provided no basis to demonstrate that the EUA should be revoked.

As explained above, section 564(g)(2) of the FD&C Act provides that FDA may revise or revoke an EUA under certain circumstances. 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.[26] The verb "may" is ordinarily permissive, particularly when the statute elsewhere uses the term "shall" to confer a mandatory duty.[27] Further underscoring FDA's discretion, the EUA statute explicitly provides that all decisions regarding EUAs are "committed to agency discretion."[28]

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,"[29] 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])."[30] Thus, in the following sections, we assess whether the Petition demonstrates that 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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[25] Petition at 4-5, 9-11.

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

[27] 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."

[28] 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].").

[29] *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).

[30] 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.[31] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564(b)(1) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)).[32]

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

The Petition does not demonstrate that the circumstances described under section 564(b)(1) no longer exist.[33] You therefore have not shown that there are grounds for revoking the authorization of the Pfizer-BioNTech COVID-19 Vaccine for individuals 5 through 11 years of age on the basis of section 564(g)(2)(A) (i.e., on the basis that the circumstances described under section 564(b)(1) no longer exist).

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

[32] COVID-19 EUA Declaration.

[33] 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 5- to 11-year-olds in order to justify an EUA." Petition at 4. We interpret Petitioner's assertion that there is "no 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 5-11 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.

Petitioner argues that there was—when FDA first authorized emergency use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 5-11 years of age—and continues to be "no emergency in this age group[,]" claiming that there is "not a severe or deadly pandemic for 5- to 11-year-old children."[34] The Petition states that, "[s]pecifically, COVID-19 would have to cause [a] serious or life-threatening disease or condition for 5- to 11-year-olds in order to justify an EUA."[35]

To the extent Petitioner's statements constitute an argument that SARS-CoV-2 cannot cause a serious or life threatening disease or condition in this population, FDA disagrees for the same reasons we provided in our response to the similar arguments in the May 2022 Petition, which we incorporate by reference.[36] The SARS-CoV-2 pandemic continues to present an extraordinary challenge to global health for the reasons discussed in the May 2022 Response and in our decision memoranda for the Pfizer-BioNTech COVID-19 Vaccine EUA, which we incorporate by reference.[37] The new information and assertions in the Petition do not change our conclusion. The Petition cites a CDC PowerPoint slide in support of the statement that deaths in 5- to 11-year-olds from COVID-19 was "extraordinary (sic) rare", but does not dispute the CDC's conclusion on the same slide that if COVID-19 associated death rates were compared to the leading causes of death in 2019, COVID-19 would have been tied for the eighth leading cause of death in children 5- to 11- years of age. The Petition also cites to an article reporting on a statement of one member who abstained from voting during the October 26, 2021 Vaccines and Related Biological Products Advisory Committee (VRBPAC) to support the position that there "was not a severe or deadly pandemic for 5- to 11-year-old children".[38] However, according to the article, that member thought "[s]ome children clearly need this vaccine" which supports the

[34] Petition at 4-5, 9-11.
[35] Id. 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 5-11 years of age.
[36] See, e.g., May 2022 Response on pages 13-15.
[37] See, e.g., id.at 13. Additional background information on the SARS-CoV-2 virus and COVID-19 pandemic may be found in FDA's decision memoranda regarding the Pfizer-BioNTech COVID-19 Vaccine EUA and FDA's decision memoranda regarding the Moderna COVID-19 Vaccine EUA. See, e.g., FDA, Pfizer-BioNTech COVID-19 Vaccine Decision Memorandum (Oct. 29, 2021) at 7-9 (providing background on COVID-19 in children 5-11 years of age); FDA, Moderna COVID-19 Vaccine Decision Memorandum (June 16, 2022) at 13-14 (providing background on COVID-19 in children under 18 years of age).
[38] Petition at 5.

fact that SARS-CoV-2 can cause a serious or life threatening disease or condition in some children in the age group.[39] In addition, the member abstained, rather than voting no on the question of whether, based on the totality of scientific evidence available, "the benefits of the Pfizer-BioNTech COVID-19 Vaccine when administered as a 2-dose series (10 µg each dose, 3 weeks apart) outweigh its risks for use in children 5-11 years of age[.]"[40] In comparison, 17 members of the Advisory Committee voted yes on that same question.

The Petition also asserts that reported "numbers related to pediatric hospitalization and death" are "inflated."[41] For example, in support of this assertion, the Petition claims that FDA "used an arbitrary rate from 'average of four weeks prior to September 11, 2021'" as the hospitalization rate.[42] The Petition claims that the "inflated" rate "had the effect of skewing the benefit risk assessment in favor of vaccination".[43] We note that, as explained in the October 29, 2021 decision memorandum, FDA used four-week averages of incidence rate for hospitalizations in COVID-NET "due to the variability in rates given the small numbers of hospitalizations per age/sex group."[44] The decision memorandum goes on to explain that the choice to use COVID-NET data to estimate the COVID-19 death rate among 5-11 year-olds instead of other national data sources for these numbers "will lead to a conservative estimate of benefits in the model."[45] Further, to account for uncertainties in the pandemic, FDA's quantitative benefit-risk analysis also modeled different scenarios, including "Scenario 3," which used a "COVID-19 incidence close to the lowest recorded incidence since the beginning of the pandemic."[46] For these reasons and the reasons discussed in section III.iv.3, we disagree with the Petitioner's claims that the benefit risk assessment was skewed in favor of vaccination.

Further, for the reasons explained in the May 2022 Response, which we incorporate by reference, the Petition appears to acknowledge that the SARS-CoV-2 virus can cause a serious or life-threatening disease or condition.[47] The data cited by Petitioner do not demonstrate otherwise; rather the citations discuss at what rates SARS-CoV-2 can cause a serious or life-threatening disease or condition.[48] 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 5-11 years of age, nor has Petitioner demonstrated that to be the case in the Petition. 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.

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[39] H. Branswell et. al, Tracking the FDA advisory panel meeting on Covid-19 vaccines for kids, STAT, Oct. 2021, https://www.statnews.com/2021/10/26/pfizer-covid19-vaccine-kids-vrbpac-fda/.

[40] See VRBPAC October 26, 2021 Meeting Summary Minutes, available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-october-26-2021-meeting-announcement#event-materials.

[41] See, e.g., Petition at 10.

[42] Id. at 10-11.

[43] Id. at 11.

[44] FDA, Pfizer-BioNTech COVID-19 Vaccine Decision Memorandum (Oct. 29, 2021), at 39.

[45] Id.

[46] Id. at 40.

[47] May 2022 Response, at 14-15.

[48] See Smith, Clare, et al., Deaths in Children and Young People in England following SARS-CoV-2 infection during the first pandemic year: a national study using linked mandatory child death reporting data, Research Square (July 7, 2021); 2 Siegel, David A., 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, MMWR (Sept. 2, 2021).

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 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 5-11 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.[49]

Petitioner raises concerns about the adequacy of clinical data relied upon to authorize the Pfizer-BioNTech COVID-19 Vaccine for emergency use in individuals 5-11 years of age.[50] Petitioner argues that "the clinical trial relied upon to authorize Pfizer's vaccine in 5- to 11-year-olds was underpowered and inadequate to properly test efficacy[.]"[51] Specifically, the Petitioner argues that the clinical trial was inadequate because "it was limited to assessing antibody levels and comparing these levels to adult levels using immunobridging."[52]

On October 29, 2021, FDA authorized the emergency use of Pfizer-BioNTech COVID-19 Vaccine for use in individuals 5-11 years of age in response to an EUA amendment request that included safety and effectiveness data from the ongoing Phase 1/2/3 randomized, observer-blinded, placebo-controlled clinical trial of the Pfizer-BioNTech COVID-19 Vaccine in which 3,109 participants 5-11 years of age have received the vaccine (Study C4591007).[53] We therefore interpret Petitioner's arguments to be in reference to this study. For the same reasons provided in the May 2022 Response to similar arguments regarding reliance on immunobridging, which we incorporate by reference, the Petition 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.[54]

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[49] FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda and Addenda. The Petition selectively quotes from FDA's May 17, 2022 Decision Memorandum regarding authorization of the Pfizer-BioNTech COVID-19 Vaccine as a booster dose in individuals 5-11 years of age, claiming that this illustrates "how lacking the data is to support use of Pfizer's vaccine in this population." Petition at 20-21. Petitioner does not explain how the quotes evidence a lack of data and ignores several portions of FDA's Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memoranda regarding use of the vaccine in individuals 5-11 years of age describing FDA's review and analysis of data relating to effectiveness. See, e.g., FDA, Pfizer-BioNTech COVID-19 Vaccine Decision Memorandum (Oct. 29, 2021) at 18-26; FDA, Pfizer-BioNTech COVID-19 Vaccine Decision Memorandum (May 17, 2022) at 10-18. Thus, the Petition's reference to FDA's May 17, 2022 Decision Memorandum fails to demonstrate that there is insufficient evidence to conclude that the Pfizer-BioNTech COVID-19 Vaccine may be effective when used to prevent COVID-19 in individuals 5 through 11 years of age.

[50] See Petition at 6-9, 11-15.

[51] Id. at 6.

[52] Id. at 7.

[53] See FDA, Pfizer-BioNTech COVID-19 Vaccine Decision Memorandum (Oct. 29, 2021) at 5.

[54] We address Petitioner's assertion that the study was underpowered in the section on Trial Size and Duration below.

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 5-11 years of age after reaching a 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.[55]

Petitioner raises concerns about the adequacy of "the clinical trial relied upon to authorize [the Pfizer-BioNTech COVID-19 Vaccine] in 5- to 11-year-olds"[56] to properly assess safety and support a benefit-risk assessment.[57] In addition, Petitioner notes post-authorization concerns related to rates of infection in vaccinated individuals, effectiveness against emerging variants, natural immunity, and numerous concerns regarding safety of the Pfizer-BioNTech COVID-19 Vaccine.[58] Due to these concerns, Petitioner argues that the EUA for the Pfizer-BioNTech COVID-19 Vaccine should be revoked with respect to individuals 5-11 years of age because "[t]he alleged benefits of Pfizer's vaccine for 5- to 11-year-olds are heavily outweighed by the known and potential risks."[59] 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 C4591007 to support FDA's benefit-risk assessment when the Agency authorized use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 5-11 years of age on October 29, 2021.[60] 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 C4591007 to assess safety.

Trial Size and Duration

The Petition asserts that because Study C4591007 "included only 2,268 participants, 1,518 of whom received the vaccine and 750 of whom received a placebo" in Cohort 1 and "included only 1,591 of whom received a vaccine and 778 of whom received a placebo" in Cohort 2, the number of participants in Study C4591007 was inadequate to detect any potential adverse event "should the

[55] 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.
[56] As explained above, we interpret this as a reference to data provided in support of the EUA amendment request from Study C4591007 for participants 5-11 years of age.
[57] Petition at 6.
[58] Id. at 11-22.
[59] Id. at 11.
[60] Id. at 6-9.

rate of injuries be less than a few in 3,109."[61] In addition, Petitioner argues that Study C4591007 was of insufficient duration because it only collected safety data for "a few months" and because there was "follow[] up with only 95.1% of cohort 1 participants."[62] To suggest that the trial was not of sufficient duration, Petitioner also points to statements in FDA's Briefing Document for the October 26, 2021 VRBPAC Meeting and a report on the results of a study of the Pfizer-BioNTech COVID-19 Vaccine in children 5-11 years of age indicating that post-authorization data "would be needed to evaluate for adverse reactions that occur too rarely to be detected in clinical trials."[63] The Petition cites statements from two members of the VRBPAC and CDC presentation slides from the November 2-3, 2021 meeting of the Advisory Committee on Immunization Practices in support of these arguments.[64, 65]

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 evaluated study plans and protocols for Study C4591007 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.[66] 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.[67] 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

[61] Id. at 6. The Petition also notes, citing an FDA Press Release, that "Pfizer's booster dose was studied in only 'approximately 400 children'" but does not otherwise make arguments specific to the booster dose portion of Study C4591007 that supported authorization of a single booster dose of the Pfizer-BioNTech COVID-19 Vaccine for children 5 through 11 years of age. See id. at 6. The basis for FDA's determination to authorize the Pfizer-BioNTech COVID-19 Vaccine for that use is set forth in FDA's Pfizer-BioNTech COVID-19 Vaccine Decision Memorandum (May 17, 2022), https://www.fda.gov/media/158575/download.

[62] Petition at 8.

[63] Id.

[64] Id. at 6. We note that the quotation attributed to Michael Kurilla should be attributed to comments from Dr. Paul Offit to reporters about the VRBPAC meeting. *See* Helen Branswell and Matthew Harper, Tracking the FDA Advisory Panel Meeting on COVID-19 Vaccines for Kids, StatNews (Oct. 26, 2021), available at https://www.statnews.com/2021/10/26/pfizer-covid19-vaccine-kids-vrbpac-fda/.

[65] FDA considered the VRBPAC discussion at the October 26, 2021 meeting when considering whether to authorize the Pfizer-BioNTech COVID-19 Vaccine in children 5 to 11 years of age, including input provided by Dr. Offit and Dr. Rubin. The Petition also fails to note that both Dr. Offit and Dr. Rubin voted "Yes" to whether the benefits of the Pfizer-BioNTech COVID-19 vaccine as a 2-dose series outweigh its risks for use in children 5 to 11 years of age. In fact, the quote from Dr. Rubin was made in explanation of his belief that "I do think we should vote to approve [the vaccine]." FDA, CBER VRBPAC Meeting Transcript (October 26, 2021), at 312.

[66] Premarketing Risk Assessment; Guidance for Industry, March 2005 at 9; https://www.fda.gov/media/71650/download.

[67] EUA Vaccine Guidance at 10-11.

apparent in the immediate post-vaccination period.[68] Adverse events considered plausibly linked to vaccination generally start within 6 weeks after vaccine receipt.[69] 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 evaluation of safety focused on data from Study C4591007 in participants 5-11 years of age who received either vaccine or placebo.[70] The available safety data to support the EUA included two Cohorts. Cohort 1 had a data cut-off of September 6, 2021 and included 2,268 individuals 5-11 years of age (1,518 in the vaccinated group and 750 in the placebo group). In Cohort 1, approximately 95% of vaccine and placebo recipients had at least 2 months of follow-up after the second dose, and >99% had follow-up for 30 days after the second dose.[71] Additional data was provided from Cohort 2. Cohort 2 had a data cut-off of October 8, 2021 and included 2,379 individuals 5-11 years of age (1,591 in the vaccinated group and 788 in the placebo group). Cohort 2 had a median duration of follow-up of 2.4 weeks after the second dose.[72] Considering that the known and potential benefits of a COVID-19 vaccine in this age group include reduction in the risk of symptomatic COVID-19 and associated serious sequelae, the safety database and duration of follow-up was appropriate and 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.

We also note that FDA's review of the EUA amendment request for use of the Pfizer-BioNTech COVID-19 Vaccine in individuals 5-11 years of age took into account safety data in individuals 12 years of age and older and post-authorization data in individuals 16 years of age and older.[73] In addition, when FDA authorized the Pfizer-BioNTech COVID-19 Vaccine for use in this population, FDA specifically recognized the possibility of "[a]dverse reactions that are very uncommon or that require longer follow-up to be detected" and noted that "[a]ctive and passive safety surveillance will continue during the post authorization period to detect new safety signals."[74] FDA has reviewed and continues to review post-authorization data in the 5-11 year-old age group, as well as post-approval and post-authorization active and passive surveillance data in all age groups, to monitor known serious risks (anaphylaxis, myocarditis, and pericarditis) and to identify any new safety concerns.

In reviewing the EUA amendment request, FDA found that Study C4591007 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

[68] 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.
[69] 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.
[70] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 5-11 Years of Age (October 29, 2021), at 32-33, https://www.fda.gov/media/153947/download.
[71] Id. at 30.
[72] Id. at 15, 30.
[73] Id. at 38-39 and 43.
[74] Id. at 39.

5-11 years of age. Petitioner has provided no information regarding the duration or size of Study C4591007 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 insufficient follow-up 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 5-11 years of age.

Trial Population

Petitioner also argues that Study C4591007 is "problematic" because it "was not representative of most American children" in that it "excluded children with immunodeficiency or autoimmune disease", excluded "children with a past virologic *or clinical* COVID-19 diagnosis" from "phase 1" and those "with a history of MIS-C or a severe adverse reaction to a vaccine."[75] The Petition further notes that "of the children receiving the vaccine, approximately 79.3% [were] White, whereas only 5.9% were Black, 21% were Hispanic or Latino, and 5.9% were Asian."[76]

FDA disagrees with the Petitioner argument that clinical data submitted to FDA were insufficiently representative to support authorization for the same reasons we provided in our response to the similar arguments in the May 2022 Petition, which we incorporate by reference.[77]

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 5-11 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 5-11 years of age.

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[75] Petition at 6-7.

[76] Id. at 7.

[77] May 2022 Response at 20-21. Petitioner's assertion regarding the phase 1 study does not change our conclusion. FDA's determination was based on the totality of available scientific evidence, not just the phase 1 portion of Study C4591007, and Petitioner fails to address why any perceived issue with the exclusion criteria in the phase 1 study is not addressed by the larger phase 2/3 portion of the study. We note that the "Phase 2/3 portion of the study did not exclude children with a history of prior SARS-CoV-2 infection or clinical symptoms/signs of COVID-19, children with known HIV, hepatitis B or hepatitis C, or stable pre-existing disease (defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment)." FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 5-11 Years of Age (October 29, 2021), at 18-19. Additionally, the fact that a study excludes some individuals from participation does not establish that the study is insufficiently representative. See, e.g., FDA, Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices and Trial Designs; Guidance for Industry at 3-4 (November 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial.

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."[78] Petitioner further asserts that "the study itself refuted the idea that vaccinating this age group would provide any real benefit" because no participants were hospitalized for COVID-19, or died from it and "therefore any adverse event, of which there were several, is of great consequence." [79]

FDA disagrees with Petitioner's argument that the clinical trial pointed to "serious issues."[80] FDA considered the rates of adverse events and serious adverse events when evaluating the known and potential benefits and risks of the vaccine for individuals 5-11 years of age.[81] FDA concluded that overall, "the rates of [solicited local and systemic] adverse reactions reported among children 5-11 years of age were lower than those reported among older age groups…"[82] With respect to serious adverse events, FDA and the study investigator considered all serious adverse events among participants unrelated to vaccination.[83]

FDA also disagrees with the Petitioner's assertion that the study demonstrated the Pfizer-BioNTech COVID-19 Vaccine would not provide "any real benefit" in 5-11 year-olds for the same reasons we provided in our response to the similar arguments in the May 2022 Petition, which we incorporate by reference.[84] For the reasons summarized in FDA's October 29, 2021, December 30, 2021, and May 17, 2022 decision memoranda, FDA determined that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweighed its known and potential risks when used to prevent COVID-19 in individuals 5-11 years of age. Petitioner has not supported its arguments that Study C4591007 raised "serious issues" or that the study demonstrated the Pfizer-BioNTech COVID-19 Vaccine would not provide "any real benefit" in 5-11 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,[85] "it became apparent that children receiving the [Pfizer-

[78] Petition at 8.
[79] Id. at 8-9.
[80] Id. at 8. The citations in the Petition do not change our determination that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh the known and potential risks. The Petition cites FDA's Briefing Document and slide presentation for the October 26, 2021 VRBPAC Meeting and Pfizer presentation slides from the November 2-3, 2021 meeting of the Advisory Committee on Immunization Practices. However, Petitioner has provided no new information to the Agency or a scientific justification in support of Petitioner's arguments, including any argument that FDA did not consider the adverse events in its determination.
[81] FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 5-11 Years of Age (October 29, 2021), at 26 - 32, https://www.fda.gov/media/153947/download.
[82] Id. at 38.
[83] Id. at 6.
[84] May 2022 Response at 23.
[85] While the Petition refers, at page 11, to a period "[a]lmost immediately after the FDA granted the EUA for use of Pfizer's vaccine in 12-to 16-year-olds in May 2021," we note that FDA first authorized the use of the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 12 through 15 years of age on May 10, 2021. We interpret the Petition to be referencing that authorization.

BioNTech COVID-19 Vaccine] can still become infected with and transmit the virus."[86] Petitioner suggests that this raises concerns regarding post-authorization effectiveness and argues that the EUA for use of the Pfizer-BioNTech COVID-19 Vaccine in this age group should thus be revoked because the current risks of the vaccine outweigh its benefits for individuals 5-11 years of age.[87] 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."[88]

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 with respect to use of the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 5-11 years of age for the same reasons we provided in our response to the similar arguments in the May 2022 Petition, which we incorporate by reference.[89] The information cited by Petitioner does not change our conclusion regarding the known and potential benefits and risks of the Pfizer-BioNTech COVID-19 Vaccine for use in this age group.

c. Effectiveness Against Emerging Variants

Petitioner argues that currently, in the 5-11 years of age population, the Pfizer-BioNTech COVID-19 Vaccine "is far below the 50% [vaccine effectiveness] threshold for EUA licensure"[90] and contends that this is, in large part, because "prior mRNA vaccination imprints

[86] Petition at 11.
[87] Id.
[88] Id.
[89] May 2022 Response, at 23-25.
[90] Petition 12. 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. We also note that "licensure" refers to approval of a BLA under the PHS Act, not issuance of an EUA under section 564 of the FD&C Act.

serological responses toward [only] Wuhan-Hu-1 rather than variant antigens."[91] Petitioner further asserts that "data is now irrefutable that Pfizer's product does not meet the necessary 50% efficacy threshold."[92] 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 5-11."[93] To suggest that FDA lacks evidence to support use of the Pfizer-BioNTech COVID-19 Vaccine in the 5-11 age group, Petitioner points to a statement in FDA's May 17, 2022 Review Memorandum that "vaccine effectiveness against COVID-19 hospitalization caused by the Omicron variant in this age group has been estimated at 68% to 74% over a median follow-up period of approximately 1 month . . ."[94] 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 effective against earlier variants, then the EUA for the Pfizer vaccine must likewise be revoked."[95] 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.[96]

First, 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,

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[91] Petition at 12. 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 "is far below the 50% [vaccine effectiveness] threshold." Petition at 12. 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. The Agency convened meetings of the VRBPAC in April and June 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; FDA, Vaccines and Related Biological Products Advisory Committee June 28, 2022 Meeting Announcement, https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-28-2022-meeting-announcement. After considering VRBPAC input, FDA advised manufacturers seeking to update their COVID-19 vaccines that they should develop modified vaccines that add an omicron BA.4/5 spike protein component to the current vaccine composition to create a bivalent booster vaccine. FDA subsequently authorized the Pfizer-BioNTech COVID-19 Vaccine, Bivalent and the Moderna COVID-19 Vaccine, Bivalent for use as a single booster dose for individuals in certain age groups as described in the respective Letters of Authorization.

[92] Petition at 13.

[93] Id. at 14.

[94] Id. at 21.

[95] Id. at 14.

[96] May 2022 Response at 26.

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 a monovalent mRNA vaccine based on the original Wuhan strain (as is the other authorized monovalent 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 monovalent 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.[97]

Results from observational studies that have investigated the effectiveness of the primary vaccination series of the Pfizer-BioNTech COVID-19 Vaccine have shown decreased effectiveness against certain variants (notably Omicron) and waning effectiveness over time.[98] Data have shown that first booster doses have restored waning vaccine effectiveness, including against severe disease and hospitalization associated with Omicron,[99] although observational studies have also indicated waning effectiveness of the first booster dose over time, mainly

[97] See CDC, COVID-19 Epidemiology and Vaccination Rates in the United States at 20-21 (June 7, 2022), https://www.fda.gov/media/159005/download; 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.

[98] 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.

[99] 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.

against mild disease, with some studies also suggesting waning effectiveness against hospitalization[100] and lower effectiveness among the immunocompromised.[101]

As previously noted in our May 2022 Petition,[102] 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.[103, 104] 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.[105] Therefore, the totality of the available scientific evidence continues to support our determination that the Pfizer-BioNTech COVID-19 Vaccine's known and potential benefits outweigh its known and potential risks for individuals 5-11 years of age. The Petition does not provide evidence showing otherwise.

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[100] 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.

[101] 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.

[102] May 2022 Response at 27.

[103] 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.

[104] In addition, a comment to the docket for this Petition (FDA-2022-P-1399) provided an article published in the New England Journal of Medicine regarding an observational study of children 5-11 years of age in Israel who received the Pfizer-BioNTech COVID-19 Vaccine during the Omicron wave, which has several limitations, but is also generally consistent with FDA's analysis regarding effectiveness against certain variants. Cohen-Stavi, et al., BNT162b2 Vaccine Effectiveness against Omicron in Children 5 to 11 Years of Age, New Eng. J. Med. 227 (July 21, 2022).

[105] 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), 36:1237-1240, 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.

With respect to Petitioner's arguments regarding monoclonal antibody treatments, for the same reasons we provided in our response to the May 2022 Petition, which we incorporate by reference, 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.[106] As discussed in our response to the May 2022 Petition, 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 at this time. [107]

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 5-11 years of age.

d. Protection Against "Long COVID"

Petitioner also argues that "one of the bases for authorization of the vaccine in this age group was prevention of 'long COVID'" but that a May 2022 study published in *Nature Medicine* "showed that vaccination provides very little protection against long COVID."[108] In addition, Petitioner cites an article from "News Medical Life Sciences" that reports on that same *Nature Medicine* publication to support the assertion that "[e]ven vaccinated people with mild breakthrough COVID-19 infections can experience debilitating, lingering symptoms that affect [several parts] of the body."[109]

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[106] May 2022 Response at 28-29.

[107] We note that on August 31, 2022, FDA revised the scope of authorization for the Pfizer-BioNTech COVID-19 Vaccine to remove its use as a booster dose for individuals 12 years and older. The revision was not based on a conclusion that the known and potential benefits of the vaccine when used as a booster dose in such individuals were outweighed by the known and potential risks. Instead, FDA determined that this revision was appropriate for the protection of the public health because FDA authorized the Pfizer-BioNTech COVID-19 Vaccine, Bivalent for use as a single booster dose in individuals 12 years of age and older to improve protection conferred by COVID-19 vaccine booster doses against the currently circulating Omicron variant of SARS-CoV-2, resulting in a more favorable anticipated benefit/risk balance compared to the Pfizer-BioNTech COVID-19 Vaccine. See FDA, Pfizer-BioNTech EUA Letter of Authorization (Aug. 31, 2022), at 13, https://www.fda.gov/media/150386/download; FDA, Pfizer-BioNTech COVID-19 Vaccine, Bivalent EUA Decision Memorandum (Aug. 31, 2022), at 15-16, https://www.fda.gov/media/161595/download. FDA revised the scope of authorization for the Moderna COVID-19 Vaccine to remove its use as a booster dose for individuals 18 years of age and older based on the same rationale. See FDA, Moderna EUA Letter of Authorization (Aug. 31, 2022), at 12, https://www.fda.gov/media/144636/download; FDA, Moderna COVID-19 Vaccine, Bivalent EUA Decision Memorandum (Aug. 31, 2022), at 16, https://www.fda.gov/media/161554/download.

[108] Petition at 13.

[109] Id. In this article, the first author of the *Nature Medicine* publication is quoted as stating, "Vaccinations remain critically important in the fight against COVID-19. *Vaccinations reduce the risk of hospitalization and dying from COVID-19*. But vaccines seem to only provide modest protection against long COVID." Henderson, E. Vaccinated people with breakthrough SARS-CoV-2 infection can experience debilitating long COVID, News Medical Life Sciences (May 25, 2022) (emphasis added).

As noted above, a vaccine does not need to be 100% effective in preventing COVID-19 for the known and potential benefits to outweigh the known and potential risks. Although Petitioner cites the *Nature Medicine* article to suggest concerns regarding post-authorization effectiveness with respect to prevention of "long COVID," the article did not, as Petitioner indicates, conclude that vaccination "provides very little protection against long COVID." Instead, the authors state that "[a]ltogether, the findings suggest that vaccination before infection confers only partial protection in the post-acute phase of [COVID-19]."[110] We note that the study also found that "[c]ompared to people with SARS-CoV-2 infection who were not previously vaccinated . . . people with [breakthrough SARS-CoV-2 infection] exhibited lower risks of death . . . and incident post-acute sequelae…"[111] Petitioner fails to demonstrate how the finding that COVID-19 vaccination confers partial protection against the risks of long COVID justifies a change in FDA's determination that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine for use in children 5-11 years of age to prevent COVID-19 outweighs its known and potential risks.

e. 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 [vaccine effectiveness] reasonably close to the 90.7% efficacy it claimed in its trial, the EUA should still be revoked in light of the real-world safety issues in 5- to 11-year-olds that were known at the time of the FDA's EUA and that have been identified since."[112]

Background on Passive and Active Surveillance

The Petition includes several arguments related to COVID-19 vaccine surveillance systems and activities, including those related to the Vaccine Adverse Event Reporting System (VAERS), Sentinel BEST (Biologics Effectiveness and Safety) System, Centers for Medicare & Medicare Services (CMS) databases, and Vaccine Safety Datalink (VSD). We incorporate by reference the summary of vaccine safety surveillance provided in the May 2022 response at 29-32.

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 5-11 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 revocation of the EUA."[113] Petitioner points to a National Vaccine Information Center webpage to show that, "VAERS data as of June 3, 2022, shows a total of 11,133 adverse events reported in 5- to 11-year-olds, of which 292 were rated as serious and 5 were deaths."[114] We also note that, like the May 2022 Petition, 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

[110] Z. Al-Aly, Long COVID after breakthrough SARS-CoV-2 Infection, Nature Medicine (July 2022), 28: 1461-1467, at 1461.
[111] Id.
[112] Petition at 15.
[113] Petition at 17.
[114] Id.

abnormal finding and a clear 'Safety Signal' that is being *knowingly* and *willfully* ignored by the CDC and FDA."[115] However, Petitioner has not provided any evidence showing that FDA is ignoring safety signals regarding COVID-19 vaccines.

As explained in our May 2022 Response, there are extensive vaccine safety surveillance efforts in place, including VAERS, for COVID-19 vaccines.[116] 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.[117] 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.[118]

It is also important to consider other factors that have contributed to the volume of VAERS reports, including the large number of COVID-19 doses administered in the United States, the v-safe system, and the concept of "stimulated reporting." We discussed these factors in the May 2022 Petition at 33-34, which we incorporate by reference.

Petitioner's arguments fail to take these factors 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 5-11 years of age, we disagree. The Petition's arguments

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[115] Id. at 18 (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."
Lindsay, et al., Letter to ACIP: "Considerations with Respect to Pediatric Populations for ACIP Meeting" November 2021, at 3, https://www.takescienceback.org/docs/2021/11/Considerations_with_Respect_to_Pediatric_Populations_for_ACIP_Meeting.pdf (emphasis in original). 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."

[116] May 2022 Response, at 33; see also FDA, COVID-19 Vaccine Safety Surveillance, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance.

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

[118] See, e.g., Pfizer-BioNTech COVID-19 Fact Sheets for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccines#additional; Moderna COVID-19 Fact Sheets for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccines#additional; 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; Novavax 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/159897/download.

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 5-11 years of age.

Petitioner's Arguments Regarding Other Surveillance Data

Petitioner also cites analyses of v-safe for the proposition that the "government's own data suggests the benefits of mass vaccination do not outweigh their risks."[119] However, the publication Petitioner cites does 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 57.5% of v-safe enrollees ages 5-11 reported local reactions and 40.9% reported systemic reactions in the week after their second dose of the Pfizer-BioNTech COVID-19 Vaccine.[120] Petitioner also notes that the analysis found that "5.1% of parents of children aged 5-11 enrolled in v-safe reported that their child was 'unable to perform normal daily activities' after dose 1 and 7.4% after dose 2."[121] But the Petition does not explain how these v-safe data demonstrate that the risks of the Pfizer-BioNTech COVID-19 Vaccine outweigh its benefits for this age group or should alter FDA's benefit-risk analysis. As stated in the cited analysis, "[t]he findings summarized in this report are similar to the safety data from preauthorization trials for Pfizer-BioNTech COVID-19 Vaccine administered to children aged 5-11 years."[122] In the cited analysis of v-safe data, approximately 1% of parents reported seeking medical care in the week after vaccination, most of which was received via a clinic appointment. We also note that among the 42,504 children aged 5-11 years enrolled in v-safe, fourteen were reported to have been hospitalized after vaccination. Whether hospitalization was the result of vaccination was not determined by the analysis and could have been due to unrelated causes temporally coincident with vaccination. All parents and guardians who reported a child's hospitalization were contacted and encouraged to complete a VAERS report.

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 5-11 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.[123] While FDA has

[119] Petition at 18.
[120] Hause, Anne M., *et al.*, *COVID-19 Vaccine Safety in Adolescents Aged 5-11 Years – United States, November 3 – December 19, 2021*, MMWR (Dec. 31, 2021), https://www.cdc.gov/mmwr/volumes/70/wr/mm705152a1.htm The v-safe data analysis found that "[t]he most frequently reported reactions after either dose were injection site pain, fatigue, and headache." Id.
[121] Petition at 18.
[122] Hause, Anne M., *et al.*, *COVID-19 Vaccine Safety in Adolescents Aged 5-11 Years – United States, November 3 – December 19, 2021*, MMWR (Dec. 31, 2021), https://www.cdc.gov/mmwr/volumes/70/wr/mm705152a1.htm
[123] Petition at 16.

carefully considered risk of myocarditis and pericarditis for vaccine recipients, including those 5-11 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, including those related to myocarditis and pericarditis in vaccine recipients. Prior to authorization of the vaccine for children 5-11 years of age, post-authorization safety surveillance reports received by FDA and CDC for the Pfizer-BioNTech COVID-19 Vaccine identified increased 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.[124]

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.[125] CDC data presented at the June 14, 2022 VRBPAC meeting showed that reporting rates to VAERS for myocarditis in children aged 5-11 years (0 to 2.6 reports per million doses administered) were much lower than the reporting rate in adolescents. The CDC data also showed that the reporting rate of myocarditis following receipt of the Pfizer-BioNTech Vaccine in male children ages 5–11 years after dose 2 of the primary series is slightly elevated when compared to background incidence but that rates are otherwise within background incidence for that age group. In addition, the CDC presentation reported that the VSD Rapid Cycle Analysis surveillance had not statistically signaled for an increased risk of myocarditis or pericarditis in children ages 5–11 years.[126] 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.[127] A survey of healthcare providers found that based on a follow-up assessment 90 days after onset of myocarditis in 398 patients ages 12-29, 81.7% of patients were reported to be fully recovered or probably fully recovered,

[124] FDA, Coronavirus (COVID-19) Update: June 25, 2021, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-june-25-2021.
[125] 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.
[126] CDC, Vaccines and Related Biological Products Advisory Committee, Update on myocarditis following mRNA COVID-19 vaccination, at slide 35 (June 14, 2022), https://www.fda.gov/media/159228/download.
[127] 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).

and an additional 15% were reported to be improved.[128] Available information suggests that most persons with myocarditis after mRNA COVID-19 vaccination recover from myocarditis by 3–8 months after diagnosis.[129]

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,[130] Petitioner asserts that FDA "utiliz[ed] an inciden[ce] rate of only 106 cases of myopericarditis cases per million children 5 to 15[.]"[131] 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[.]"[132] The Petitioner also cites a "Hong Kong study", which it argues "determined that 37 per 100,000 males aged 12-17 were diagnosed with myocarditis following their second Pfizer COVID-19 shot."[133] As we explain in our response to similar arguments in the May 2022 Petition, which we incorporate by reference, incidence rates can vary across data sources.[134] This is especially the case when data sources come from different populations. For the same reasons we provided in our response to the similar arguments in the May 2022 Petition, which we incorporate by reference,[135] the Petition 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.

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."[136] The article Petitioner cites does not support the proposition for the reasons provided in our May 2022 Response, which is incorporated by reference.[137] 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."

Petitioner also 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

[128] CDC, CDC Advisory Committee on Immunization Practices, Myocarditis following mRNA COVID-19 vaccination (slide presentation) at slide 13 (July 19, 2022), https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-07-19/03-COVID-Shimabukuro-508.pdf.
[129] Id. at slide 26. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-07-19/03-COVID-Shimabukuro-508.pdf.
[130] 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.
[131] Petition at 16.
[132] Id.
[133] Id. at 16-17.
[134] May 2022 Response at 36-37.
[135] Id. at 36-39.
[136] Petition at 13.
[137] May 2022 Response at 39.

result in serious chronic conditions consistent with other forms of myocarditis."[138] In support of this statement, the Petition cites a CDC presentation to ACIP and notes that "in at least one case, [vaccine-induced myocarditis] has resulted in the death of a young male".[139] The cited CDC presentation discussed reports to VAERS of myocarditis after Pfizer-BioNTech vaccination among children ages 5-11 years,[140] and we have addressed the limitations of VAERS, including with respect to determining causality, in previous sections of this response.

As noted in our May 2022 Response, 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, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management,[141] FDA agrees that it is important to monitor and gain a better understanding of long-term outcomes and factor new information into benefit-risk assessments. We described steps being taken to help address these questions in the May 2022 Response at 39-41, which we incorporate by reference.

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, with the highest observed risk in adolescent males, 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 5-11 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

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[138] Petition at 17. 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. This article 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 5-11 years of age for the reasons described in the response to the May 2022 Petition. May 2022 Response, at 40, n. 182. Petitioner goes on to cite five other publications for the proposition that "[n]umerous studies since have confirmed the seriousness of myocarditis." Petition at 17 n.97. The cited publications 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 5-11 years of age for the same reasons provided in our response to the similar arguments in the May 2022 Petition. See May 2022 Response at 40, n. 182.

[139] Petition at 17.

[140] CDC, COVID-19 Vaccine Safety Updates: Primary Series in Children Ages 5-11 years (May 19, 2022), https://stacks.cdc.gov/view/cdc/117469.

[141] 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.

diverse adverse consequences to human health.'"[142] The Petition repeats the same arguments regarding this "study" as made in the May 2022 Petition. We addressed those arguments at pages 41-42 of the May 2022 Response, which we incorporate by reference. Additionally, the Petition cites an article for the proposition that "estimates show that we must accept 4 reports of fatal and 16 reports of serious side effect per 100,000 vaccinations in order to save the lives of 8 to 33 people…we would have to accept that 2 people might die to save the lives of three to 15 people."[143] The article cited by the Petition has since been retracted from scientific journal publication due to "misinterpretation of data, leading to incorrect and distorted conclusions."[144]

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 ('ADE'). Some experts also fear that doing so will lead to highly infectious and highly virulent variants of SARS-CoV-2 that will be

[142] Petition at 18.
[143] Id. at 18-19; Walach, *et al.*, *The Safety of COVID-19 Vaccinations—Should We Rethink the Policy?*, Science, Public Health Policy, and the Law (Aug. 2021), https://www.publichealthpolicyjournal.com/_files/ugd/adf864_8c97b2396c2842b3b05975bfbd8254cb.pdf.
[144] The cited article was retracted from publication in *Vaccines* after "concerns were brought to the attention of the publisher regarding misinterpretation of data, leading to incorrect and distorted conclusions." An evaluation by members of the Editorial Board found that the article "contained several errors that fundamentally affect the interpretation of the findings." See Retraction: Walach, et al., The Safety of COVID-19 Vaccinations—We Should Rethink the Policy, Vaccines 2021, 9(7):729. https://doi.org/10.3390/vaccines9070729.

resistant to any spike-based COVID-19 vaccines."[145] The statements from Dr. Geert Vanden Bossche cited in the Petition do not support this proposition for the same reasons described at page 42 of our May 2022 Response, which we incorporate by reference.[146, 147]

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.[148] For the same reasons discussed in our response to this argument in the May 2022 Petition, which we incorporate by

[145] Petition at 19.

[146] The Petition also references a letter focused on EUA of COVID-19 vaccines for use in children 5 years of age and under from certain members of Congress to FDA Commissioner Robert Califf, which noted that "[w]orld renowned immunologists have raised concerns about the possibility of antibody dependent enhancement." Petition at 20. This letter cites one review article in support of this statement. This article does not conclude that individuals vaccinated against COVID-19 are experiencing antibody dependent enhancement; instead, it concludes that "careful design and testing of [COVID-19] vaccines will be necessary to evaluate which viral mutations can escape from antibodies-mediated neutralization as well as which one significantly affects the efficacy of the currently approved vaccines." See Sánchez-Zuno et al. A review: Antibody-dependent enhancement in COVID-19: The not so friendly side of antibodies. *Int J Immunopathol Pharmacol*. 2021; 35:20587384211050199. doi:10.1177/20587384211050199. FDA has considered these issues and recognized the importance of issues related to the optimal strain composition for COVID-19 vaccines to address current and emerging and emerging SARS-CoV-2 variants, including when and how frequently to consider composition changes to address variants. See *supra* note 91.

[147] Petition at 19. 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."). To further support this assertion, Petitioner references a February 2022 article "illustrat[ing] that infectivity strengthening mutations were the main mechanism for viral evolution, while vaccine-escape mutations become a dominating viral evolutionary mechanism among highly vaccinated populations." Wang, et al., Emerging Vaccine-Breakthrough SARS-CoV-2 Variants, ACS Infectious Disease (Feb. 8, 2022) 8: 546-556. https://pubs.acs.org/doi/10.1021/acsinfecdis.1c00557. The authors of this article state that their objective "is to forecast SARS-CoV-2 variants that pose an imminent threat to combatting COVID-19 and long term public health…" The authors identify sets of mutations that "have a high likelihood of massive growth…[and] predict that they can escape existing vaccines." While the authors "foresee an urgent need to develop new virus combatting strategies" they do not conclude that continued COVID-19 vaccination will "lead to highly infectious and highly virulent variants of SARS-CoV-2 that will be resistant to any spike-based COVID-19 vaccines" as the Petition states.

[148] Petition at 19.

reference,[149] these data do not demonstrate that "the fully vaccinated have been suffering Antibody Dependent Enhancement" as Petitioner argues.[150, 151]

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 5-11 years of age.

Petitioner's Claims Regarding "Natural Immunity"

The Petition argues that "[t]he issue of waning immunity due to variants is all the more significant since the superior protective effect of natural immunity is now beyond dispute."[152] The Petition appears to make arguments related to "natural immunity" to say that this "immunity" causes the benefits of vaccination to be "far smaller than the FDA's benefit-risk assessment accounted for," [153] such that the known and potential benefits of the Pfizer-BioNTech COVID-19 Vaccine do not outweigh the known and potential risks.[154] 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.[155]

The Petition's arguments regarding "natural immunity" do not undermine the benefit-risk analysis supporting FDA's authorization. To the extent those arguments repeat the assertions made in the May 2022 Petition, FDA disagrees for the same reasons we provided in our response to the similar arguments in the May 2022 Petition, which we incorporate by reference.[156] The Petition also asserts that FDA's "benefit-risk assessment did not make any adjustments for those

[149] May 2022 Response at 43.
[150] 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 20. 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.")
[151] 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 20. 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.
[152] Petition at 14.
[153] Id. at 22.
[154] Id. at 14-15.
[155] 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.
[156] See, e.g., May 2022 Response on pages 44-46.

children who already had superior protective immunity from prior infection."[157] In support of this assertion, the Petition refers to the transcript of the October 26, 2021 meeting of the VRBPAC (which it inaccurately refers to as the "ACIP meeting"). In that transcript, the FDA presenter explained that the Agency had considered all children 5-11 years of age to be susceptible to disease because it did not have data in this age group to establish how protection against COVID-19 for individuals 5-11 years of age who test positive for SARS-CoV-2 would compare to protection offered by the Pfizer-BioNTech COVID-19 Vaccine.[158] Petitioner claims that FDA's position is "dubious" because "by September 2021, there were over sixty studies suggesting natural immunity was equal to if not superior to vaccine-induced immunity."[159] However, to support this claim, Petitioner cites two letters it sent to the CDC director. Petitioner does not indicate which studies it is referring to in the letters nor does it explain how any of those studies demonstrate that "natural immunity was equal to if not superior to vaccine-induced immunity" in children 5-11 years of age.[160]

The Petition also attempts to demonstrate that the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risk in children 5-11 years of age by mischaracterizing a quotation from the October 26, 2021 VRBPAC meeting transcript to support Petitioner's own benefit-risk calculation purporting to show that vaccination would cause more ICU stays than it would prevent.[161] That claim is not supported by the quotation from the VRBPAC transcript.[162] As exemplified by the exchange in the transcript Petitioner highlights, the VRBPAC was aware of data presented on seropositivity in children 5-11 years of age and its members had the opportunity to consider the impact of natural immunity in assessing the benefits and risks of the Pfizer-BioNTech COVID-19 Vaccine in children 5-11 years of age.[163] The VRBPAC agreed that "[b]ased on the totality of scientific evidence available," the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweighed the risks for use in children 5-11 years of age, with 17 members voting in agreement, 1 member abstaining, and no members disagreeing with that statement.[164]

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 5-11 years of age, outweighs its known and potential risks.

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[157] Petition at 15.
[158] VRBPAC October 26, 2021 Meeting Transcript at 256-258. At the time the analysis was conducted, there was limited data on the strength and waning of natural immunity. This limitation of the analysis and was discussed during the FDA presentation.
[159] Petition at 15.
[160] Id.
[161] Id.
[162] The Petition claims that the FDA presenter "acknowledged during the October 26, 2021 ACIP meeting, if 45% of children in the 5- to 11-year-old age group had protective antibodies from prior infection '[t]hen basically, you have 45 percent reduction of the other benefit, *i.e.*, a 45% reduction of the benefit of the vaccine." Id. at 15-16. Petitioner fails to note that the statement about a "45 percent reduction of the other benefit" was hypothetical and expressly prefaced by an assumption that if "individuals . . . test positive in antibodies, they have the same kind of the protection as the vaccine." VRBPAC October 26, 2021 Meeting Transcript at 256-58. During the same exchange, the FDA presenter explained that it was not clear how seropositivity affects protection from COVID-19. Id.
[163] October 29, 2021 Decision Memo at 41-42.
[164] Id.

f. 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 5-11 years of age 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 5-11 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.

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 5-11 years of age on the grounds that there is an adequate, approved, and available alternative for 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 12 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 5-11 years of age. The criterion under section 564(c)(3) of the FD&C Act is met.

v. The Petition Does Not Provide Other Bases that 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.[165]

FDA determined the EUA standard is met for the Pfizer-BioNTech COVID-19 Vaccine in individuals 5-11 years of age because data submitted by the sponsors demonstrated in a clear and compelling manner that the known and potential benefits of this vaccine, when used to prevent COVID-19, outweigh the known and potential risks in such individuals, and that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating COVID-19 in this population.

FDA finds no basis in the information submitted in the Petition to support a revocation of the Pfizer-BioNTech COVID-19 Vaccine EUA for use in individuals 5-11 years of age.[166] As described above, the Petition has not provided information demonstrating that that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine for this population are outweighed by its known and potential risks. Furthermore, Petitioner has not demonstrated that other circumstances make a revision or revocation of the EUA for the Pfizer-BioNTech COVID-19 Vaccine for use in individuals 5-11 years of age appropriate to protect the public health or safety. FDA therefore sees no justifiable basis upon which to take any action based on the Petition regarding the Pfizer-BioNTech COVID-19 Vaccine EUA for use in individuals 5-11 years of age. Accordingly, as noted above, we deny Petitioner's request that FDA "revoke the June 17, 2022 reissuance of the EUA letter of authorization for the use of Pfizer-BioNTech's COVID-19 [V]accine for children ages 5 through 11."

[165] EUA Guidance at 29.

[166] As noted above, on August 31, 2022, FDA revised the EUA for the Pfizer-BioNTech COVID-19 Vaccine to authorize a single booster dose of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 12 years and older and to remove the use of COMIRNATY and the Pfizer-BioNTech COVID-19 Vaccine for use as a booster dose for individuals 12 years of age and older. Pfizer and BioNTech have publicly announced that they have submitted an EUA amendment request to FDA for emergency use authorization of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent for use as a booster dose in individuals 5-11 years of age. Pfizer, "Pfizer and BioNTech Submit Application to U.S. FDA for Emergency Use Authorization of Omicron BA.4/BA.5-Adapted Bivalent Vaccine Booster in Children 5 Through 11 Years of Age" (September 26, 2022), https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-submit-application-us-fda-emergency-0. Should FDA decide to revise the scope of authorization for the Pfizer-BioNTech COVID-19 Vaccine to remove its use as a booster dose in individuals 5-11 years of age, it would not be because the Petition demonstrates that the known and potential benefits of the vaccine are outweighed by its known and potential risks when used as a booster dose in that age group or because the Petition demonstrates that any other statutory basis for revocation or revision of the EUA applies.

B. Petitioner's Request that FDA Revoke the June 17, 2022 Emergency Use Authorization for the Use of Moderna's COVID-19 Vaccine in Individuals Ages 6 Years through 11 Years

In this section, we address Petitioner's request that "the June 17, 2022 reissuance of the EUA letter of authorization for the use of Moderna's COVID-19 vaccine in children ages 6 through 11 be provoked [sic] pursuant to 21 U.S.C. § 360bbb-3(g)."[167] In support of this request, the Petition states that "[f]or the same reasons set forth above, Moderna's vaccine presents a far greater risk than benefit to 6- to 11-year-olds, particularly since Moderna's vaccine presents an even higher risk profile to this age group than Pfizer's vaccine."[168] We interpret the reference to "the same 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 5-11 years of age. Therefore, to the extent such arguments apply to the Moderna COVID-19 Vaccine for use in individuals 6 years -11 years of age, we incorporate our above responses to those arguments in this section.

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, including on June 17, 2022, when the EUA was amended to authorize the use of the Moderna COVID-19 Vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months through 17 years of age.[169] Currently, the Moderna COVID-19 Vaccine[170] 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.

On August 31, 2022, the EUA was amended to authorize the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) for the prevention of COVID-19 in individuals 18 years of age and older as a single booster dose administered at least 2 months after either:

- completion of primary vaccination with any FDA authorized or approved monovalent COVID-19 vaccine, or

[167] Petition at 3.
[168] Id. at 20.
[169] 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 is posted on www.fda.gov.
[170] 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.

- receipt of the most recent booster dose with any FDA authorized or approved monovalent 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,[171] and the data upon which it was based, in detail. [172]

ii. The Standard for Revocation of EUAs Is Not Met

In the following sections we address whether the Petition demonstrates that any of the statutory conditions under which FDA may revoke an EUA are met with respect to the Moderna COVID-19 Vaccine for use in individuals 6 years-11 years of age, namely: (1) whether the circumstances described under section 564(b)(1) of the FD&C Act no longer exist, (2) whether the criteria 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.

iii. Circumstances Described under Section 564(b)(1) of the FD&C Act Continue to Exist

For the reasons described in section III.A.iii of this response with respect to Petitioner's arguments regarding the Pfizer-BioNTech COVID-19 Vaccine, the Petition does not demonstrate 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

This section describes why the Petition has not demonstrated that the criteria under section 564(c) of the FD&C Act are no longer met with respect to the Moderna COVID-19 Vaccine for use in individuals 6 years-11 years of age. 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 6 years-11 years of age. Thus, the criterion in section 564(c)(1) of the FD&C Act is satisfied. The Petition does not state that the Moderna COVID-19 Vaccine fails to meet this criterion. However, to the

[171] 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; June 16, 2022; and August 31, 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.

[172] 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.

extent the Petition argues that the criterion in section 564(c)(1) of the FD&C Act is not met, 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 6 years-11 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.[173] Additionally, descriptive efficacy analyses for each age cohort (12 through 17 years, 6 years through 11 years, 2 through 5 years, and 6 months through 23 months) 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).[174] The descriptive efficacy estimates were primarily based on mild COVID-19 cases. Vaccine efficacy against severe disease is expected to be higher compared to vaccine efficacy against non-severe COVID-19 as observed in the adult clinical trial and in real world studies.[175]

With respect to its request that FDA revoke the EUA letter of authorization for the Moderna COVID-19 Vaccine for use in individuals 6 years-11 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 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 6 years-11 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],

[173] FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (June 16, 2022) ("Moderna June 17, 2022 Decision Memorandum"), at 10, https://www.fda.gov/media/159611/download.
[174] Id. at 176.
[175] Id.

outweigh the known and potential risks of the product . . . ." Petitioner asserts that the "known benefits of Moderna's vaccine for 6- to 11-year-olds do not outweigh the known and potential risks" citing concerns related to the size of Moderna's clinical trial and risks of myocarditis.[176]

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 4,016 participants in part 2, only 2,998 of whom received the vaccine."[177] 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 6 years-11 years of age were insufficient in size, Petitioner updated the number of participants to reflect those in Moderna's trial in 6 years-11 years of age, but otherwise the Petition does not provide new information to support these arguments with respect to the Moderna COVID-19 Vaccine. Therefore, the Petition does not demonstrate the trial was underpowered or insufficient in size for the reasons described in section III.A.iv.3 and the reasons describing FDA's authorization decision in FDA's decision memorandum.[178]

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 6 years-11 years of age] are even more significant than those of the Pfizer vaccine."[179] 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."[180] The study at issue examined the risks of myocarditis and pericarditis in "residents aged 12 years or older."[181] The study 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."[182] The study did not evaluate the risk of myocarditis or pericarditis in the 6 year to 11-year-old age group.

Petitioner also references a March 2021 statement from the European Medical Association (EMA)[183] 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

[176] Petition at 23.
[177] Id. at 22.
[178] Moderna June 17, 2022 Decision Memorandum, https://www.fda.gov/media/159611/download.
[179] Petition at 22.
[180] Id.
[181] 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.
[182] Id.
[183] 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.

"[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)."[184, 185] Petitioner cited these same sources in the May 2022 Petition, and the Petition provides no other data to support the claim that "[t]he risks of the Moderna vaccine to [individuals 6 years-11 years of age] are even more significant than those of the Pfizer vaccine."[186]

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 COVID-19 vaccines, as explained in our response to similar arguments in May 2022 Petition, which we incorporate by reference.[187] In addition, as explained in the June 17, 2022 decision memorandum, available real world data on the Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine suggest a lower risk in the 6 years-11 years age group compared with individuals 12-24 years of age.[188] Based on the totality of the available scientific evidence, the evidence regarding myocarditis/pericarditis risks does not create an unfavorable benefit-risk profile for use of the Moderna COVID-19 Vaccine to prevent COVID-19 in individuals 6 years-11 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 6 years-11 years of age. 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 revoke authorization of Moderna COVID-19 Vaccine for use in individuals 6 years-11 years of age on the grounds that there is an adequate, approved, and available alternative for 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 12 years of age and older. Spikevax is approved for the prevention of COVID-19 in individuals 18 years of age or older.

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[184] 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.

[185] 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 22. 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.

[186] Id.

[187] May 2022 Response at 52-53.

[188] Moderna June 17, 2022 Decision Memorandum at 178-179.

There are no COVID-19 vaccines that are approved to provide a COVID-19 vaccination in individuals younger than 12 years of age. Therefore, there are no adequate, approved, and available alternatives to the Moderna COVID-19 Vaccine for individuals 6 years-11 years of age. The criterion under section 564(c)(3) of the FD&C Act is met.

v. The Petition Does Not Provide Other Bases that Make a Revision or Revocation Appropriate to Protect the Public Health or Safety

For the reasons described above and in FDA's June 17, 2022 Decision Memorandum, FDA determined the EUA standard is met for the Moderna COVID-19 Vaccine when used to prevent COVID-19 in individuals 6 years-11 years of age. FDA finds no basis in the information submitted in the Petition to support a revocation of the Moderna COVID-19 Vaccine EUA for use in this population. As described above, the Petition has not provided information demonstrating that that the known and potential benefits of Moderna COVID-19 Vaccine in individuals 6 years-11 years of age are outweighed by its known and potential risks. Furthermore, Petitioner has not demonstrated that other circumstances make a revision or revocation of the EUA for the Moderna COVID-19 Vaccine for use in individuals 6 years-11 years of age appropriate to protect the public health or safety. FDA therefore sees no justifiable basis upon which to take any action based on the Petition regarding the Moderna COVID-19 Vaccine EUA for use in individuals 6 years-11 years of age. Accordingly, we deny your request that FDA revoke the June 17, 2022 reissuance of the EUA letter of authorization for the use of Moderna's COVID-19 vaccine in children 6 years-11 years of age.[189]

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."[190] 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."[191] For the reasons described in FDA's May 2022 Response addressing the same request,[192] which we incorporate by reference, 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. Basic scientific research is necessary to assess the contribution of T-cell responses to protection. FDA therefore denies the request to require sponsors to include such assessments in clinical investigations of vaccines for prevention of COVID-19.

[189] Petition at 3.
[190] Id.
[191] 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.
[192] May 2022 Response at 56.

IV. CONCLUSION

FDA has considered Petitioner's requests to revoke the EUA for use of the Pfizer-BioNTech COVID-19 Vaccine in children ages 5 through 11 years; revoke the EUA for the use of the Moderna COVID-19 Vaccine in children ages 6 years through 11 years; 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