April 18, 2023

Linda Wastila
Coalition Advocating for Adequately Labeled Medicines (CAALM)
220 Arch Street
Baltimore, MD 21201

Sent via email to: lsimoniw@rx.umaryland.edu

RE: Citizen Petition (Docket Number: FDA-2023-P-0360)

Dear CAALM:

This letter responds to the citizen petition (the Petition) dated January 31, 2023 that you (Petitioner) submitted to the Food and Drug Administration (FDA, the Agency, we) requesting that FDA "require that the sponsors of Comirnaty, Spikevax, Pfizer-BioNTech COVID-19 Vaccine, and Moderna COVID-19 Vaccine (collectively, 'Pfizer and Moderna COVID-19 vaccines') amend current product labeling"[1] "for all authorized or approved indications and populations"[2] to:

> "1. Add language clarifying that phase III trials were not designed to determine and failed to provide substantial evidence of vaccine efficacy against SARS-CoV-2 transmission or death.
> 2. Add language clarifying that the immunobridging surrogate endpoint used in multiple authorized indications has not been validated to predict clinical efficacy.
> 3. Add safety and efficacy results data from manufacturer randomized trials of current bivalent boosters that reported results after EUA was granted.
> 4. Add a clear statement that FDA authorized a new Pfizer vaccine formulation containing Tris buffer without requiring clinical studies to evaluate efficacy, safety or bioequivalence to the formulation containing phosphate buffer.
> 5. Add a clear statement disclosing that a Pfizer phase III randomized trial in pregnant women (NCT04754594) was completed as of July 2022 but there have been no results reported.
> 6. Add a clear statement that Pfizer vaccine efficacy wanes after 2 months following dose 2 according to the Pfizer phase III randomized trial.
> 7. The following adverse event types should be added to the Adverse Reactions section of labeling:
>
> a. multisystem inflammatory syndrome (MIS) in children;
> b. pulmonary embolism;

[1] Petition at 1.
[2] *Id*.

c. sudden cardiac death;
d. neuropathic and autonomic disorders.

8. The following reproductive health and lactation related adverse event types should be added to the Adverse Reactions section of labeling:
   a. decreased sperm concentration;
   b. heavy menstrual bleeding;
   c. detection of vaccine mRNA in breastmilk.
9. Add frequency data for clinical and subclinical myocarditis.
10. Labeling should present trial results on serious adverse events in tables with statistics, as is done for non-serious adverse events."

The Petition also requests that the "FDA create a Medication Guide and communicate these labeling changes via a Dear Health Care Provider (DHCP) letter."

This letter responds to the Petition in full. We have carefully reviewed the Petition and other information available to the Agency. Having reviewed these materials, and for the reasons described below, we are granting one of your requests related to revisions to the labeling for one vaccine to describe updated clinical trial data regarding the vaccine. However, for the reasons described below, we conclude that the Petition does not contain facts demonstrating any reasonable grounds for the other 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 these other requests in the Petition.

Here is an outline of FDA's response:

I. BACKGROUND

There is currently a pandemic of respiratory disease, COVID-19, caused by a novel coronavirus, SARS-CoV-2. The COVID-19 pandemic presents an extraordinary challenge to global health. The Secretary of the Department of Health and Human Services (HHS) has determined that there is a public health emergency, or a significant potential for a public health emergency, related to COVID-19. [3] In addition, the Secretary of HHS has declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic. [4]

[3] *See* HHS, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3., 85 FR 7316 (February 4, 2020); https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency. *See also* HHS, Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b) ("Amended Determination")., 88 FR 16644 (March 15, 2023); https://www.federalregister.gov/documents/2023/03/20/2023-05609/covid-19-emergency-use-authorization-declaration.

[4] *See* HHS, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3., 85 FR 18250 (April 1, 2020); https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration. *See also* Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that

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[5] vaccines sponsored by Pfizer Inc. (Pfizer),[6] ModernaTX, Inc. (Moderna),[7] Novavax Inc. (Novavax), and JanssenBiotech, Inc. (Janssen)[8], as well as bivalent[9] vaccines sponsored by Pfizer[10] and Moderna.[11] The EUAs have been amended since initial issuance and remain in place.

Since the original issuance of these EUAs, FDA has also approved two COVID-19 vaccines that had previously been authorized under EUA. 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.[12][13] 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.[14] Spikevax is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Today, we are revising the EUAs to simplify the vaccination schedule for most individuals. This includes authorizing the current bivalent COVID-19 vaccines (Original and Omicron BA.4/BA.5) to be used for all doses administered to individuals 6 months of age and older.

Because the Petition requests that FDA amend the labeling of "Pfizer and Moderna COVID-19 vaccines," this response focuses on the following vaccines manufactured by those companies that are authorized and approved for use in the United States: Comirnaty (COVID-19 Vaccine, mRNA), Spikevax (COVID-19 Vaccine, mRNA), the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5), and the Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5). For ease of communication, we use the same shorthand for these vaccines that is used in the Petition: "the Pfizer and Moderna COVID-19 vaccines."

---

circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

[5] For the purposes of this letter, 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.

[6] Hereinafter "Pfizer-BioNTech COVID-19 Vaccine".

[7] Hereinafter "Moderna COVID-19 Vaccine".

[8] Hereinafter "Janssen COVID-19 Vaccine".

[9] For the purposes of this letter, unless otherwise specified, bivalent refers to any FDA authorized COVID-19 vaccine that encodes the spike protein of the Original SARS-CoV-2 and the Omicron BA.4/BA.5 SARS-CoV-2.

[10] Hereinafter "Pfizer-BioNTech COVID-19 Vaccine, Bivalent".

[11] Hereinafter "Moderna COVID-19 Vaccine, Bivalent."

[12] BioNTech Manufacturing GmbH is the biologics license holder for this vaccine, which is manufactured by Pfizer for BioNTech Manufacturing GmbH.

[13] The Aug. 23, 2021BLA Approval Letter for Comirnaty is available at: https://www.fda.gov/media/151710/download .

[14] The Jan. 31, 2022 BLA Approval Letter for Spikevax is available at https://www.fda.gov/media/155815/download.

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.[15] Before a vaccine is licensed (approved) by FDA for use by the public, FDA requires that it undergo a rigorous and extensive development program to determine the vaccine's safety and effectiveness. This development program encompasses preclinical research (laboratory research, animal studies[16]) and clinical studies. At the preclinical stage, the sponsor focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies. Clinical studies, in humans, are conducted under well-defined conditions and with careful safety monitoring through all the phases of the investigational new drug process. FDA's regulations governing the conduct of clinical investigations are set out at 21 CFR Part 312.

B. Licensed Vaccines Are Safe, Pure, and Potent

FDA has a stringent regulatory process for licensing vaccines.[17, 18] 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."[19] 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, purity, and potency before FDA will consider licensing the vaccine. FDA requires that the sponsor's application include, among other things, data derived from nonclinical and clinical studies showing the product's safety, purity, and potency; a full description of manufacturing methods for the product; data establishing the product's stability through the dating period; and representative sample(s) of the product and summaries of results of tests performed on the lot(s) represented by the sample.[20]

As is evident from the language of the PHS Act and FDA's regulations, the licensure process for a vaccine requires the sponsor to establish, through carefully controlled laboratory and clinical studies, as well as through other data, that the product is safe and effective for its proposed uses. FDA's multidisciplinary review teams then rigorously evaluate the sponsor's laboratory and clinical data, as well as other information, to help assess whether the safety, purity, and potency

---

[15] See 21 CFR 312.2(a) (explaining that the regulations in 21 CFR Part 312 apply to clinical investigations of both drugs and biologics).

[16] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[17] 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.

[18] FDA, Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.

[19] Section 351(a)(2)(C)(i)(I) of the PHS Act.

[20] 21 CFR 601.2(a).

of a vaccine have been demonstrated.[21] Only when FDA's standards are met is a vaccine licensed.

FDA regulations explicitly state that "[a]pproval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products."[22] Therefore, the manufacturers of vaccines that have been licensed in the U.S. have necessarily demonstrated the safety, purity, and potency of the vaccines within the meaning of the applicable statutory and regulatory provisions before the vaccines were licensed and allowed to be marketed.

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

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

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

For additional background about FDA's EUA authority, see FDA's guidance document, "Emergency Use of Medical Products and Related Authorities: Guidance for Industry and Other Stakeholders" (January 2017).[23]

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

a. EUA for Pfizer's and BioNTech's COVID-19 Vaccines

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 has since been amended to authorize various booster dose uses of the Pfizer-BioNTech COVID-19 Vaccine, expand the populations who are authorized to receive the vaccine, and authorize the use of Pfizer-BioNTech COVID-19 Vaccine, Bivalent in individuals 6 months of

[21] FDA, Vaccines, last updated February 2023, https://www.fda.gov/vaccines-blood-biologics/vaccines.
[22] 21 CFR 601.2(d).
[23] *See* Emergency Use of Medical Products and Related Authorities; Guidance for Industry and Other Stakeholders, January 2017, (EUA Guidance), https://www.fda.gov/media/97321/download.

age and older, among other revisions.[24] Today, we are revising the EUA to authorize the current bivalent COVID-19 vaccines (including the Pfizer-BioNTech COVID-19 Vaccine, Bivalent) to be used for all doses administered to individuals 6 months of age and older . For each revision to the EUA, FDA conducted a thorough review of the relevant information and data to determine that the use of the vaccine meets the statutory requirements under section 564 of the FD&C Act, and FDA explained its evaluation of the data in materials that the Agency made available to the public.[25]

b. EUA for Moderna's COVID-19 Vaccines

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 has since been amended to authorize various booster dose uses of the Moderna COVID-19 Vaccine, expand the populations who are authorized to receive the vaccine, and authorize the Moderna COVID-19 Vaccine, Bivalent in individuals 6 months of age and older, among other revisions.[26] Today, we are revising the EUA to authorize the current bivalent COVID-19 vaccines (including the Moderna COVID-19 Vaccine, Bivalent) to be used for all doses administered to individuals 6 months of age and older. For each revision to the EUA, FDA conducted a thorough review of the relevant information and data to determine that the use of the vaccine meets the statutory requirements under section 564 of the FD&C Act and explained its evaluation of the data in materials that the Agency made available to the public.[27]

D. Standards for Labeling

i. Labeling Requirements for Approved Biological Products Generally

The labeling requirements for approved prescription drugs and biological products derive from several sections of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the PHS Act, including: Sections 201, 502, and 503 of the FD&C Act and section 351 of the PHS Act. FDA regulations govern the content and format of prescription drug labeling for approved drugs and biological products.[28] These regulations are intended to organize labeling information to more effectively communicate to health care professionals the "information necessary for the safe and effective use of prescription drugs."[29] FDA regulations further require that the labeling for most

---

[24] For a description of all revisions to the EUA, see Pfizer-BioNTech COVID-19 Vaccine Letter of Authorization, March 14, 2023. This Letter of Authorization is posted on www.fda.gov.

[25] For example, FDA has posted its review memorandum explaining each EUA authorization on the Agency's website, available at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine. This letter incorporates by reference the EUA Review Memoranda, which discuss these determinations, and the data upon which they were based, in detail.

[26] For a description of all revisions to the EUA, see Moderna COVID-19 Vaccine Letter of Authorization, December 8, 2022. This Letter of Authorization is posted on www.fda.gov.

[27] For example, FDA has posted its review memorandum explaining each EUA authorization on the Agency's website, available at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/spikevax-and-moderna-covid-19-vaccine. This letter incorporates by reference the EUA Review Memoranda, which discuss these determinations, and the data upon which they were based, in detail.

[28] See, e.g., 21 CFR 201.56 and 21 CFR 201.57; see also 21 CFR 201.100(c).

[29] Preamble to final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922 at 3928, January 24, 2006) (Physician Labeling Rule). For the content and format

prescription drugs include, among other information, the following sections: Contraindications; Warnings and Precautions; Adverse Reactions; Indications and Usage; Clinical Studies; and Use in Specific Populations. A prescription drug, including a prescription biological product such as a vaccine, is misbranded if its labeling is false or misleading in any particular.[30]

A prescription drug product's FDA approved Prescribing Information (also sometimes referred to by terms including ''professional labeling,'' ''package insert,'' ''direction circular,'' or ''package circular'') is a compilation of information about the product, approved by FDA, based on the agency's thorough analysis of the new drug application (NDA) or BLA submitted by the applicant. It is written for the health care practitioner audience, because prescription drugs require ''professional supervision of a practitioner licensed by law to administer such drug."[31] Prescribing information for a vaccine is based on scientific data that are submitted by the manufacturer in the BLA and determined by the FDA to be satisfactory to support the approved indication(s), usage, dosing, and administration.[32] The labeling must be updated when new information becomes available that causes the labeling to be inaccurate, false or misleading.[33]

As relevant to the licensed vaccines that are the subject of the Petition, required information and the specific format for labeling of approved prescription drugs and biological products are set out in FDA regulations at 21 CFR §§ 201.56 and 201.57. Under 21 CFR § 201.57(c)(2), the Indications and Usage section of the full prescribing information must "state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition." For biological products, indications "must be supported by substantial evidence of effectiveness."[34] The Clinical Studies section of a vaccine's labeling discusses those clinical studies that facilitate an understanding of how to use the vaccine safely and effectively, and this section will describe the studies that support effectiveness for the vaccine's labeled indication(s).[35]

In addition, FDA regulations in 21 CFR § 201.57(c)(2)(ii) provide that "[i]f there is a common belief that [a] drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section [the Indications and Usage section of the product's prescribing information] state that there is a lack of evidence that the drug is effective or safe for that use or condition."

---

requirements for the labeling of older prescription drug products that are not subject to the labeling requirements in § 201.57, see § 201.80 (21 CFR 201.80). The specific labeling requirements for older drug products differ in certain respects, and generally are not referenced in this response. The licensed vaccines that are the subject of this Petition are subject to the requirements in § 201.57.

[30] See section 502(a) of the FD&C Act; see also 21 CFR 201.56(a)(2).

[31] 21 U.S.C. 353(b).

[32] See FDA, Vaccine Development-101, last updated December 2020, https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-development-101.

[33] 21 CFR 201.56(a)(2).

[34] 21 CFR 201.57(c)(2)(v).

[35] 21 CFR 201.57(c)(15).

Medication Guides may be another component of the FDA-approved labeling. Medication Guides apply primarily to human prescription drug products used on an outpatient basis without direct supervision by a healthcare professional and are applicable to both new and refill prescriptions.[36] Section 208.1(c) states that a Medication Guide will be required if FDA determines one or more of the following circumstances exist: (1) The drug product is one for which patient labeling could help prevent serious adverse effects; (2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, the product; and (3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. Under part 208, Medication Guides may be safety-related, addressing serious risk(s) (relative to benefits) of which patients should be made aware, and/or efficacy-related, when patient adherence to directions for use is crucial to the drug's effectiveness.[37]

FDA reviews and approves the labeling of prescription biological products as part of its approval of a BLA and after approval continues to assess the adequacy of labeling.

ii. Labeling Requirements for EUA Products

For EUA products, section 564 of the FD&C Act provides that to the extent practicable given the circumstances of the emergency, FDA is to establish certain conditions as the agency finds necessary or appropriate to protect the public. In particular, section 564 provides for FDA (to the extent practicable given the circumstances of the emergency) to establish conditions to ensure that health care professionals who administer the EUA product are informed:

- That FDA has authorized the emergency use of the product (including the product name and an explanation of its intended use);
- Of the significant known and potential benefits and risks of the emergency use of the product, and the extent to which such benefits and risks are unknown; and
- Of available alternatives and their benefits and risks.[38]

In addition, section 564 also provides for information for recipients of EUA products. In particular, section 564 provides for FDA (to the extent practicable given the circumstances of the emergency) to ensure that recipients are informed:

- That FDA has authorized emergency use of the product;
- Of the significant known and potential benefits and risks associated with the emergency use of the product, and of the extent to which such benefits and risks are unknown;
- That they have the option to accept or refuse the EUA product and of any consequences of refusing administration of the product; and

[36] 21 CFR 208.1(a).
[37] 21 CFR 208.1(b) and (c).
[38] See section 564(e)(1)(A)(i)) of the FD&C Act (pertaining to unapproved products) and section 564(e)(2)(A) of the FD&C Act (pertaining to unapproved uses of approved products).

- Of any available alternatives to the product and of the risks and benefits of available alternatives.[39]

Consistent with the statute, the EUAs for the Pfizer and Moderna COVID-19 vaccines have imposed these informational conditions by requiring the distribution to healthcare providers and vaccine recipients of authorized labeling in the form of Fact Sheets with implementing language. For example, the fact sheets for recipients and caregivers describe the emergency use authorization and describe the vaccine's risks and benefits. The fact sheets are required to be distributed to vaccine recipients under the EUA, and they are also publicly available for viewing on FDA's website.

III. DISCUSSION

A. Petitioner's Request that FDA Amend Current Labeling to Address Transmission

Petitioner requests that FDA "amend current labeling of Pfizer and Moderna COVID-19 vaccines (for all authorized or approved indications and populations)" to "add language clarifying that phase III trials were not designed to determine and failed to provide substantial evidence of vaccine efficacy against SARS-CoV-2 transmission."[40]

Although the Petition concedes that "labeling that states what a product has not been proven to do is uncommon," the Petition asserts that "[t]here is a widespread (but inaccurate) notion that efficacy against infection and transmission have been established by substantial evidence, and that these vaccines contribute to herd immunity."

In support of this claim, the Petition points to statements by various U.S. government officials. Specifically, the Petition identifies a statement by President Biden that "you're not going to get COVID;"[41] a statement by Dr. Anthony Fauci that "when you become vaccinated… you become a dead end to the virus;"[42] and a statement by Dr. Rachelle Walensky that "vaccinated people do not carry the virus[.]"[43] The Petition also identifies a statement in the Clinical Review Memo for Comirnaty that lists, among a substantial list under the heading "Evidence and Uncertainties," the following: "Public health vaccination goals of immunizing 75% of the population (to achieve herd immunity) have not yet been achieved."[44] Finally, the Petition identifies statements made by the two companies. In a Pfizer briefing document submitted to FDA's VRBPAC, the

---

[39] See section 564(e)(1)(A)(ii) of the FD&C Act (pertaining to unapproved products) and section 564(e)(2)(A) of the FD&C Act (pertaining to unapproved uses of approved products).

[40] Petition at 1. Your request in the Petition goes on to state, "or death." However, in the portion of the Petition devoted to this request, you do not provide any explanation as to why the labeling should be amended to state that the Pfizer and Moderna COVID-19 vaccines do not prevent death. Your argument about the need for the labeling to correct an alleged misimpression is limited to your argument that there is a widespread misbelief that the Pfizer and Moderna COVID-19 vaccines prevent transmission. We deny the request regarding death because you have not provided a justification for the request. *See* 21 CFR 10.30(b)(3) (requiring citizen petitions to provide a statement of grounds for the requested action).

[41] Petition at 4.

[42] *Id.*

[43] *Id.*

[44] https://www.fda.gov/media/152256/download#page=95

company stated: "Maximizing the proportion of the population that is vaccinated is critically important to help reduce rates of infection, decrease transmission, prevent the emergence of new variants of concern, and hasten the end of the pandemic."[45] In a statement that previously appeared on Moderna's website (but now seems to be available only through the "wayback" Internet archive), the company stated: "To safely achieve herd immunity against COVID-19, a large amount of a population needs to be vaccinated."[46] This statement appears in a section of the webpage devoted to "Helpful Terms to Know," and under a subheading devoted to the term "Herd immunity." Finally, the Petition points to the regulation in 21 CFR 201.57(c)(2)(ii) that provides that FDA may require a labeling statement that there is a lack of evidence that a drug is effective or safe for a use or condition when there is a "common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks[.]"[47]

Your Petition does not persuade us that a revision to the labeling is needed. As discussed further in the paragraphs that follow, your proposed statement for inclusion in the labeling is not required by statute or regulation and we are not convinced by your arguments that the change is necessary for the safe and effective use of the vaccines.

It is important to note that FDA's authorization and licensure standards for vaccines do not require demonstration of the prevention of infection or transmission. A vaccine can meet the licensure standard if the vaccine's benefits of protecting against disease outweigh the vaccine's risks for the licensed use. There is no requirement that the vaccine also prevents infection with the pathogen that can cause the disease or transmission of that pathogen to others.[48] Similarly, a vaccine can meet the EUA standard without any evidence that the vaccine prevents infection or transmission. To that end, there is no requirement that the clinical trials supporting a vaccine's licensure or authorization be designed to determine whether the vaccine prevents infection of a pathogen or transmission of that pathogen to others. In addition, with respect to the discussion of clinical studies in prescription drug labeling, FDA's regulations require that the clinical studies

[45] https://www.fda.gov/media/153409/download#page=16

[46] http://web.archive.org/web/20230107040800/https:/www.makeityourvaccine.com/faqs.

[47] The Petition also points to the Warnings and Precautions section of the Tamiflu labeling, which includes a statement that: "Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. TAMIFLU has not been shown to prevent such complications." However, the Petition has not demonstrated that the considerations that led to this statement being added to the Tamiflu labeling are applicable to the labeling for the Pfizer and Moderna COVID-19 vaccines. Just because a "has not been shown" statement is included in the Tamiflu labeling does not mean that such a statement must be added to the labeling for the Pfizer and Moderna COVID-19 vaccines.

[48] We note that a vaccine does not need to be 100% effective in preventing the target disease in order to meet the licensure standard. It is expected that some vaccinated individuals will contract the target disease despite having been vaccinated against it. No FDA licensed or authorized vaccine is 100% effective in preventing disease, but scientific data has nevertheless demonstrated that vaccinations have been a very effective approach to protecting the public's health in the U.S. (See FDA, Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.)

section of labeling must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively.[49] [50]

After undergoing a rigorous and comprehensive scientific and regulatory process to demonstrate that the relevant statutory and regulatory requirements are satisfied, the Pfizer and Moderna COVID-19 vaccines have been licensed or authorized for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2. This is directly stated in the relevant labeling for each product—in the Indications and Usage section of the Prescribing Information for the approved products, and on the first page of the healthcare provider and recipient Fact Sheets for the authorized products.[51] The vaccines are not licensed or authorized for prevention of infection with the SARS-CoV-2 virus or for prevention of transmission of the virus, nor were the clinical trials supporting the approvals and authorizations designed to assess whether the vaccines prevent infection or transmission of the virus. In the clinical trials supporting the initial authorization of the vaccines, the primary efficacy endpoint was incidence of COVID-19, i.e. incidence of the disease caused by the SARS-CoV-2 virus. Specifically, for the Pfizer-BioNTech COVID-19 Vaccine, the primary efficacy endpoint was incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before or during the 2-dose vaccination regimen,[52] and for the Moderna COVID-19 Vaccine the primary efficacy endpoint was the reduction of incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before the first dose of vaccine in the period after 14 days post-dose 2.[53] These studies are accurately described in the authorized and approved labeling for the Pfizer and Moderna COVID-19 vaccines. For example, Table 24 in the most current Fact Sheet for healthcare providers administering the Pfizer-BioNTech COVID-19 Vaccine, Bivalent[54] presents this vaccine efficacy information, describing data about the first COVID-19 occurrence from 7 days after dose 2. As another example, Table 3 in the Spikevax Prescribing Information presents efficacy of the vaccine against COVID-19 in participants 18 years of age and older starting 14 days after dose 2.

The Petition's assertion that there is a "widespread (but inaccurate) notion that efficacy against infection and transmission have been established by substantial evidence" is supported only by references to selected statements by U.S government officials suggesting that vaccination against COVID-19 may prevent infection or transmission, as well as one statement from Pfizer and one

---

[49] 21 CFR 201.57(c)(15)).

[50] Although the labeling for EUA products is not subject to the regulation in 21 CFR 201.57, the Petition makes the same request and same arguments with respect to the approved labeling and the EUA labeling for these COVID-19 vaccines. Because of this, and because it would be appropriate for this this type of labeling information to be consistent across labeling for these EUA and BLA COVID-19 vaccine products, we evaluate the requested labeling revision to the approved labeling and the EUA labeling for these products under the same analysis.

[51] The Package Inserts for the licensed vaccines are available at the following website links: for Spikevax- https://www.fda.gov/media/155675/download, for Comirnaty https://www.fda.gov/media/151707/download, and https://www.fda.gov/media/154834/download. The authorized Fact Sheets are available on FDA's website for each authorized vaccine.

[52] See FDA, Pfizer-BioNTech COVID-19 Vaccine, Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum, (Dec. 11, 2020), *available at* https://www.fda.gov/media/144416/download.

[53] FDA, Moderna COVID-19 Vaccine, Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum, (Dec. 18, 2020), *available at https://www.fda.gov/media/144673/download*.

[54] This fact sheet is entitled, Fact Sheet for Healthcare Providers Administering Vaccine: Emergency Use Authorization of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).

from Moderna. Your Petition also does not account for countervailing statements made by some of these officials. For example, Dr. Fauci has stated that the vaccines were not developed to protect against infection,[55] and Dr. Walensky has stated that high viral loads in vaccinated individuals "suggest an increased risk of transmission[.]"[56] In responding to your Petition, we are not agreeing or disagreeing with any of the statements that are selected in the Petition. Rather, we are observing that the statements referenced by the Petition do not demonstrate a commonly held belief that the clinical trials provided substantial evidence of efficacy against SARS-CoV-2 transmission. We are not convinced that there is any widespread misconception about this.

The Petition's request also implicates the issue of how clinical studies data should be described in vaccine labeling. Under FDA's regulations for prescription drug labeling, the clinical studies section "must discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively."[57] The regulation further provide that, "[o]rdinarily, this section will describe the studies that support effectiveness for the labeled indication(s), including discussion of study design, population, endpoints, and results, but must not include an encyclopedic listing of all, or even most, studies performed as part of the product's clinical development program."[58] It is notable that the regulation provides for the labeling to address endpoints that were studied—but does not provide for the labeling to address endpoints that were *not* studied. There are many reasons why a vaccine clinical trial might study a disease endpoint, but not a transmission endpoint. For example, a disease endpoint may in some cases be more feasible to assess, compared to a transmission endpoint. Furthermore, the applicable statutory standards for licensure and authorization of vaccines do not require that the primary objective of efficacy trials be a demonstration of reduction in person-to-person transmission. The Petition points to no statutory or regulatory requirement for labeling to state that a clinical trial did not address an endpoint that is not included in the labeled indication. Moreover, the Petition does not persuade us that the description of the clinical studies in the authorized and approved labeling misrepresents the endpoints that were assessed. In fact, the authorized and approved labeling accurately describes the clinical studies.

In short, the authorized fact sheets and Prescribing Information of the licensed vaccines are consistent with the applicable statutory and regulatory requirements in that they accurately describe the approved indications or authorized uses of these vaccines and present data related to these indications/uses.[59] For Comirnaty and Spikevax, the Indications and Usage section of the prescribing information describes each vaccine's indication (active immunization against coronavirus disease 2019) and data to support these indications are accurately described in the Clinical Studies section. Similarly, for the EUA vaccines, the fact sheets for healthcare

---

[55] *See* Sarah Jacoby, "Early COVID-19 Vaccines May Prevent Symptoms but not the Infection, Dr. Fauci Says," Self, Oct. 29, 2020, *available at* *https://www.self.com/story/early-covid-19-vaccines-prevent-symptoms* (quoting Dr. Fauci as stating "[t]he primary endpoint is to prevent clinical disease, to prevent symptomatic disease, not necessarily to prevent infection" and "The primary thing you want to do is, if people get infected, prevent them from getting sick. And if you prevent them from getting sick you will ultimately prevent them from getting seriously ill, so that's what we want to do").

[56] CDC, Statement from CDC Director Rochelle P. Walensky, MD, MPH on Today's MMWR, (July 30, 2021), https://www.cdc.gov/media/releases/2021/s0730-mmwr-covid-19.html.

[57] 21 CFR 201.57(c)(15).

[58] *Id.*

[59] See 21 CFR 201.57(c)(2); section 564(e) of the FD&C Act.

providers and recipients and caregivers state that the vaccines have received emergency use authorization to permit the use of the vaccines to prevent COVID-19. The fact sheets also include information about the benefits and risks of the vaccines and accurately describe the supporting clinical studies. The current labeling therefore clearly sets forth the approved indication or authorized use, as applicable, and accurately describes the supporting clinical studies.

For all of the above-described reasons, we deny the request for the labeling for the Pfizer and Moderna COVID-19 vaccines to be revised to state that the clinical trials were not designed to determine and did not provide substantial evidence of efficacy against SARS-CoV-2 transmission.

B. Petitioner's Request that FDA Add Labeling Regarding Immunobridging Surrogate Endpoint Validation

Petitioner requests that FDA "[a]dd language clarifying that the immunobridging surrogate endpoint used in multiple authorized indications has not been validated to predict clinical efficacy."[60] The Petitioner claims that "FDA has granted multiple EUAs on the basis of trials that used an immunobridging primary efficacy endpoint (neutralizing antibody titers)"[61] and that "[t]his immunobridging surrogate endpoint has not been validated to predict clinical efficacy."[62]

In support of this request, the Petition points to FDA's regulation that is codified in 21 CFR 201.57. The Petition states that the regulation requires that "drugs approved on a surrogate endpoint must include 'a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits.'"[63] The Petition states that "FDA has granted multiple EUAs on the basis of trials that used an immunobridging primary efficacy endpoint," and that "[w]hile current labeling includes immunobridging efficacy results data, current labeling does not state that this endpoint has not been validated to predict clinical efficacy, as required by 21 CFR 201.57."

The Petition misunderstands FDA's regulation. The Petition relies on a portion of the regulation, 21 CFR 201.57(c)(2)(1)(B), that pertains to drugs that are granted accelerated approval based on a surrogate endpoint. This is clear from the regulatory text, the relevant part of which states that it applies "if the indication is approved based on a surrogate endpoint under § 314.510 or § 601.41." Those provisions – § 314.510 or § 601.41 – are provisions that apply to the accelerated approval of drugs and biological products, respectively. The regulatory text in 21 CFR 201.57(c)(2)(1)(B) goes on to state that for drugs that are approved under those provisions, such drugs must include, in the Indications and Usage section of the labeling, "a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the 'Clinical Studies' section for a discussion of the relevant evidence."[64] The accelerated approval process is one of several approaches used by the FDA to

[60] Petition at 5.
[61] *Id.*
[62] *Id.*
[63] *Id.*
[64] 21 CFR 201.57(c)(2)(i)(B).

expedite the development of drugs for serious or life-threatening diseases and conditions.[65] But the Pfizer and Moderna COVID-19 vaccines have not been approved under the accelerated approval pathway, so the regulatory provision excerpted in the Petition does not apply to the labeling for the Pfizer and Moderna COVID-19 vaccines. Because the basis for the Petition's request is a regulation that does not apply to the labeling of the Pfizer and Moderna COVID-19 vaccines, the Petition has not supported the requested action. We therefore deny the request.

At the same time, we wish to point out that the authorized and approved labeling for the Pfizer and Moderna COVID-19 vaccines includes accurate descriptions of the data supporting the marketing of the vaccines.

C. Petitioner's Request That FDA Amend Current Labeling to Add Safety and Efficacy Data From Certain Trials of Bivalent COVID-19 Vaccines

The Petition requests that FDA add information to the EUA labeling for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent and Moderna COVID-19 Vaccine, Bivalent. Specifically, the Petition requests that FDA add "safety and efficacy results data from manufacturer randomized trials of current bivalent boosters that reported results after EUA was granted."[66] The Petition states that on August 31, 2022, when FDA first issued EUAs for those vaccines, the "vaccine formulations had not completed any human testing."[67] The Petition further states that after the EUA was granted, "Pfizer and Moderna both reported results in press releases of Phase 2/3 randomized trials[.]"[68] The Petition continues that "[a]t present, labeling (Section 18 Clinical Trial Results and Supporting Data for EUA: Pfizer p.36, Moderna p.36) does not mention these trials or any other clinical trials of Bivalent (Original and Omicron BA.4/BA.5) vaccines,"[69] and that the labeling "should be updated to reflect current data."

Because the clinical trial data that is the subject of the press releases cited in the Petition were not available when FDA authorized the bivalent vaccines on August 31 for individuals 12 years of age and older (Pfizer-BioNTech COVID-19 Vaccine, Bivalent) and 18 years of age and older (Moderna COVID-19 Vaccine, Bivalent), the EUA labeling authorized at the time did not include information about these clinical results. Since August 31, FDA has authorized the bivalent COVID-19 vaccines for younger age groups, and in doing so the agency has included available relevant clinical results in the age-specific labeling that the Agency authorized as part of its review of the use of the bivalent COVID-19 vaccines for these younger age groups.

Today, FDA is updating the EUAs to authorize the bivalent formulations of the vaccines in accordance with an updated dosing regimen, and in doing so we are consolidating the EUA

[65] Section 506(c) of the FD&C Act provides that the FDA may grant accelerated approval to "a product for a serious or life-threatening disease or condition upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

[66] Petition at 6.

[67] *Id.*

[68] *Id.*

[69] *Id.*

labeling so that there are no longer age-specific fact sheets. With today's action, for each vaccine, the Pfizer-BioNTech COVID-19 Vaccine, Bivalent and the Moderna COVID-19 Vaccine, Bivalent, we are authorizing a single healthcare provider fact sheet that covers all authorized age groups. These consolidated fact sheets include information about the available relevant clinical data, including a presentation in the healthcare provider fact sheet for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent of safety data that is referenced in the Pfizer press release. Therefore, insofar as the Petition is requesting a presentation of the information described in this fact sheet, we grant the request with respect to the changes the Petition requests in the EUA fact sheet for healthcare providers regarding the Pfizer-BioNTech COVID-19 Vaccine, Bivalent.

With respect to the Moderna press release that the Petition references, FDA has not conducted an evaluation of the data that is referenced in the press release. Because FDA conducts its own evaluation of a sponsor's clinical trial data included in a request as part of the process for authorizing a vaccine and its use under an EUA, those data are not included in the consolidated EUA fact sheet for the Moderna COVID-19 Vaccine, Bivalent. Consistent with section 564(e)(1)(A)(i)-(ii) of the FD&C Act, the fact sheets that FDA is authorizing under the Moderna EUA ensure that healthcare providers and vaccine recipients and caregivers are informed of the significant known and potential benefits and risks of the emergency use of the product, and the extent to which such benefits and risks are unknown and of the alternatives to the product that are available.[70] The Petition does not explain how the Moderna EUA fact sheets violate any statutory or regulatory requirement. The Petition also does not explain how the fact sheets are inaccurate, false, or misleading by virtue of not addressing this specific data. Because the Petition fails to support the requested action, and because the authorized Moderna fact sheets meet all applicable statutory requirements, we deny the request with respect to the data addressed in the Moderna press release.

D. Petitioner's Request That FDA Amend Current Pfizer Vaccine Labeling Regarding Tris Buffer and Phosphate Buffer and Clinical Trials

The Petition requests that FDA revise the labeling to include "a clear statement that FDA authorized a new Pfizer vaccine formulation containing Tris buffer without requiring clinical studies to evaluate efficacy, safety or bioequivalence to the formulation containing phosphate buffer."[71] The Petition states that because certain clinical trials of the Pfizer-BioNTech COVID-19 Vaccine were conducted with the vaccine manufactured with phosphate-buffered saline (PBS), the labeling for the Pfizer COVID-19 vaccines should bear a "clear statement . . . stating that the authorized or approved indications containing a Tris buffer is for a formulation that was not studied in these trials."[72]

[70] The authorized Moderna COVID-19 Vaccine Fact Sheets are also consistent with section 564(e)(1)(A)(i)-(ii) of the FD&C Act in that they provide information that the Secretary has authorized the emergency use of the vaccine; they describe alternatives; and for the fact sheet for vaccine recipients and caregivers, the fact sheet provides information about the option to accept or refuse administration of the product and the consequences, if any, of refusing administration of the product.

[71] *Id.*

[72] Petition at 7.

This request relates to FDA's October 29, 2021 EUA action in which FDA authorized: 1) the use of Pfizer-BioNTech COVID-19 Vaccine for children 5 through 11 years of age; and 2) a manufacturing change to include an additional formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses tromethamine (Tris) buffer instead of phosphate buffered saline (PBS) used in the originally authorized Pfizer-BioNTech COVID-19 Vaccine. The formulation of the Pfizer-BioNTech COVID-19 Vaccine that uses Tris buffer was authorized on October 29, 2021 in two presentations: 1) multiple dose vials, with gray caps and labels with a gray border, formulated to provide, without need for dilution, doses (each 0.3 mL dose containing 30 microgram (mcg) nucleoside-modified messenger RNA (modRNA)) for individuals 12 years of age and older; and 2) multiple dose vials, with orange caps and labels with an orange border, formulated to provide, after dilution, doses (each 0.2 mL dose containing 10 mcg modRNA) for individuals 5 through 11 years of age.[73]

As explained in the October 29, 2021 Letter of Authorization[74] and the Review Memorandum accompanying the authorization,[75] FDA authorized this manufacturing change to provide a vaccine with an improved stability profile and greater ease of use at vaccine distribution sites. Analytical comparability assessment, which uses laboratory testing to demonstrate that a change in product formulation is not expected to impact safety or effectiveness of the product, demonstrated that the Tris/Sucrose formulation is comparable to the previously authorized/ approved PBS/Sucrose formulation. Multiple different release parameters were evaluated to assess the comparability of the modified formulation (the formulation with the Tris buffer) to the originally authorized formulation (the formulation with the PBS buffer). These release parameters ranged from product appearance to size of the lipid-nanoparticle to the integrity of the modRNA in the product. Additionally, characterization testing was performed to evaluate product composition and purity, including characteristics of the modRNA, as these are characteristics associated with the activity of the vaccine. The combination of release testing and characterization testing demonstrated that the modified formulation is analytically comparable to the original formulation. FDA explained this testing and the manufacturing change in the October 29, 2021 Letter of Authorization[76] and the Review Memorandum accompanying the authorization,[77] both of which the Agency made available on its website.

However, FDA did not include detailed information about the data supporting the manufacturing change in the accompanying Fact Sheets.[78] Prescription drug labeling is a communication tool.

---

[73] Since then, FDA has authorized the formulation of the Pfizer-BioNTech COVID-19 Vaccine using Tris buffer in additional presentations, and FDA has also authorized the use Pfizer-BioNTech COVID-19 Vaccine, Bivalent that uses Tris buffer. In addition, on December 16, 2021 FDA approved a request from Pfizer to supplement the company's BLA to include a new 30 microgram dose formulation (Tris/Sucrose) of Comirnaty and on the same day also approved corresponding labeling revisions.

[74] See Letter of Authorization, October 29, 2021, reissued March 14, 2023, *available at* https://www.fda.gov/media/150386/download

[75] See Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum, October 29, 2021 *available at* https://www.fda.gov/media/153947/download

[76] See Letter of Authorization, October 29, 2021, reissued March 14, 2023, *available at* https://www.fda.gov/media/150386/download

[77] See Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum, October 29, 2021 *available at* https://www.fda.gov/media/153947/download.

[78] Similarly, when Pfizer updated its approved labeling to reflect the new Tris formulation, FDA approved the labeling without information detailing the data that supported the manufacturing change.

Its principal objective is to make available to healthcare providers the detailed prescribing information necessary for the safe and effective use of a drug, in a manner that is clear and useful to providers when prescribing for and counseling patients.[79] Labeling information about the data supporting the manufacturing change would not contribute to the safe and effective use of the vaccine. FDA's review of the data supporting the manufacturing change ensured that the manufacturing change was not expected to impact safety or effectiveness of the product, and including information about the data supporting the manufacturing change would not further the safe and effective use of the vaccine. What was relevant to healthcare providers was how the manufacturing change impacted the actual use of the vaccine. Specifically, the different formulations necessitated different instructions for use. For individuals 12 years and older the PBS formulation of the Pfizer-BioNTech COVID-19 Vaccine required dilution prior to use, while the Tris buffer formulation did not. FDA ensured that the labeling information for healthcare providers clearly conveyed these different instructions for use. But FDA does not agree with the Petition's request that the labeling should address the data supporting the manufacturing change. Notably, the Petition fails to identify any statutory or regulatory requirement that labeling must describe the data supporting a manufacturing change. The Petition also fails to explain why including this information in the labeling would contribute to the safe and effective use of the vaccine, and why the absence of this information in the labeling causes the labeling to be false, inaccurate, or misleading. For all of these reasons, we deny the request.

E. Petitioner's Request That FDA Amend Current Pfizer Vaccine Labeling to State That Results From a Phase 3 Clinical Trial in Pregnant Women Have Not Been Reported

The Petition points to a Pfizer trial of pregnant women that began in February 2021[80] for which, according to the Petition, no results have been reported in the publicly available literature. The Petition states that while Section 8.1 of the Comirnaty labeling describes animal data about the use of Comirnaty during pregnancy,[81] the labeling does not address this particular clinical trial. The Petition requests that "a clear statement disclosing that a Pfizer phase III randomized trial in pregnant women (NCT04754594) was completed as of July 2022 but there have been no results reported."

As support for the request, the Petition points only to the fact that the clinical trial was reported to have been started, but that no results from the trial are publicly available. FDA's labeling regulations generally require prescription drug labeling to include a subsection that contains information on what is known about the drug's effect on pregnancy.[82] This includes a risk summary that describes the risk of adverse developmental outcomes based on all relevant human data, animal data, and/or the drug's pharmacology.[83] It is notable that the regulation requires that the labeling address relevant data, but does not require that the labeling address the fact that

[79] See 21 CFR 201.56(a)(1) (providing that prescription drug labeling "must contain a summary of the essential scientific information needed for the safe and effective use of the drug").
[80] Information about the trial is publicly available at https://clinicaltrials.gov/ct2/show/NCT04754594.
[81] Similar information is also included in the Pfizer-BioNTech COVID-19 Fact Sheets for Healthcare Providers Administering Vaccine (Vaccination Providers), available at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccines#additional.
[82] 21 CFR 201.57(c)(9)(i)-(iii).
[83] 21 CFR 201.57(c)(9)(i)(B).

a study may have been started but results were not reported. The Petition fails to explain how including the fact of no results being reported would be relevant information that would contribute to the safe and effective use of the vaccine.[84] There are many reasons why a clinical trial might be started but results not reported, some of which may not bear on the safety of a drug. For example, a clinical trial could be started but not completed due to a sponsor's inability to enroll enough human subjects. A sponsor might have particular difficulty enrolling subjects if potential subjects can access the drug outside of a clinical trial, such as when the drug is already marketed. Because the Petition points to no statutory or regulatory requirement for labeling to state that a clinical trial was started but the results were not reported, and because the Petition fails to explain the relevance of such information, we deny the request.

F. Petitioner's Request That FDA Amend Current Labeling Regarding Pfizer Vaccine Efficacy After 2 Months Following Dose 2

The Petition requests that the labeling for the Pfizer vaccines be amended to provide "a clear statement that Pfizer vaccine efficacy wanes after 2 months following dose 2 according to the Pfizer phase III randomized trial."[85] In support of this request, the Petition points to results from a single study. Specifically, the Petition states that "[c]urrent labeling makes no mention of the data from Pfizer's phase 3 randomized trial showing (a) that efficacy is variable over time and (b) declines following an early peak."[86]

Monovalent mRNA-based vaccines from Moderna and Pfizer-BioNTech are based on the original (ancestral) strain of SARS-CoV-2 and initially had effectiveness of up to 90 to 95% against symptomatic disease when the ancestral strain was circulating. However, a succession of viral variants and waning of individual immunity led to a reduction in vaccine effectiveness over time. In the setting of the viral variants that have emerged, boosting with vaccines based on the ancestral strain was able to restore some degree of protection against serious and symptomatic disease, but it appeared that effectiveness against symptomatic disease declined more rapidly than that against serious disease.[87] To address the rapid global spread of the Omicron variant, along with clinical trial and real-world data indicating waning protection following primary series and booster doses of the original (monovalent) COVID-19 vaccines, and reduced effectiveness of the original (monovalent) COVID-19 vaccines against Omicron, FDA recommended that manufacturers develop bivalent COVID-19 vaccines that include a component based on the original strain and a component based on Omicron BA.4/BA.5 for use

---

[84] One of FDA's goals in approving or authorizing labeling is to ensure that the labeling contains information necessary for the safe and effective use of a drug or biological product. See 21 CFR 201.56(a)(1) (providing that prescription drug labeling "must contain a summary of the essential scientific information needed for the safe and effective use of the drug"); 564(e)(A)(1)(i)-(ii) of the FD&C Act (providing that to the extent practicable given the applicable circumstances the Secretary shall establish conditions on an authorization as the Secretary finds necessary or appropriate, including appropriate conditions designed to ensure that healthcare providers and recipients are informed of the significant known and potential benefits and risks of the product).

[85] Petition at 8.

[86] *Id.*

[87] *See* discussion of waning immunity in: FDA, Pfizer-BioNTech COVID-19 Vaccine, Bivalent Emergency Use Authorization (EUA) Amendment for an Unapproved Product Review Memorandum (March 14, 2023), https://www.fda.gov/media/166240/download.

as a booster dose potentially beginning in fall 2022. FDA next took action to authorize bivalent vaccines, first on August 31, 2022 and most recently with today's EUA action.

These recent EUA actions were based in part on a recognition of waning protection following vaccination with the original (monovalent) COVID-19 vaccines. Therefore, FDA does not dispute the premise of the Petition's request, i.e. the premise that there is evidence of waning of protection. However, the Petition does not explain why the requested labeling statement is needed to ensure that the labeling is not false, inaccurate, or misleading. The Petition also does not explain why the labeling statement is needed in light of the actions FDA has taken to authorize bivalent vaccines and also in light of the following statement that is currently included in the EUA fact sheets for recipients and caregivers: "The duration of protection against COVID-19 is currently unknown." This fact sheet statement already addresses the fact that the duration of protection from vaccination is unknown. For these reasons, we deny the request.

G. Petitioner's Request That FDA Amend Current Labeling to Add Certain Additional Adverse Reactions

- **i.** Multisystem inflammatory syndrome (MIS) in children
- **ii.** Pulmonary embolism
- **iii.** Sudden cardiac death
- **iv.** Neuropathic and autonomic disorders

The Petition states that "[t]he following adverse event types should be added to the Adverse Reactions section of labeling:" multisystem inflammatory syndrome (MIS) in children; pulmonary embolism ("Pfizer only"); sudden cardiac death; and neuropathic and autonomic disorders.

In support of this request, the Petition states that since the introduction of the COVID-19 vaccines, "there has been a dramatic increase in reports to the Vaccine Adverse Event Report System (VAERS)." The Petition further points to several scientific publications that the Petition describes as supporting these requests. These include a publication in the *Lancet* related to MIS in children; a publication in *Vaccine* related to pulmonary embolism; certain autopsy reports related to sudden cardiac death; and an NIH study related to neuropathic and autonomic disorders. The Petition further states that a "causal relationship does not need to be established before adding adverse events to the label that are detected in the postmarketing period" (emphasis in original).

FDA's regulation related to the Adverse Reactions section of approved labeling states that the section must describe the "overall adverse reaction profile of the drug based on the entire safety database."[88] The regulation further provides that "an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence."[89] Finally, the regulation provides that this definition "does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug

[88] 21 CFR 201.57(c)(7).
[89] *Id.*

and the occurrence of the adverse event."[90] FDA decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: seriousness of the event, number of reports, or strength of causal relationship to the drug/vaccine. Decisions on whether there is some basis to believe there is a causal relationship are a matter of medical and scientific judgment and are based on factors such as: the frequency of reporting, biological plausibility, the timing of the event relative to the time of vaccination, and whether the adverse event is known to be caused by related vaccines. For more information about the Agency's policy with respect to the adverse reaction section of drug and vaccine labeling, see "Guidance for Industry: Adverse Reactions Section of Labeling for Human and Prescription Drug and Biological Products – Content and Format."[91] In general, the Adverse Reactions section of labeling includes only information that would be useful to healthcare practitioners making treatment decisions and monitoring and advising patients. Although the Petition asserts that a "causal relationship does not need to be established before adding adverse events to the label," this assertion appears to overlook the relevant regulatory criteria. The definition of an adverse reaction does not include all adverse events observed during use of a drug. It is limited to those events for which there is some basis to believe there is a causal relationship between occurrence of an adverse event and the use of a drug (§ 201.57(c)(7)).

The scientific sources the Petition cites do not support the requested actions. Specifically:

- The Petition points to an increase in VAERS reports as support for the proposed additions to the Adverse Reactions section of the labeling. VAERS is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed or authorized in the United States. Passive surveillance is defined as unsolicited reports of adverse events that are sent to a central database or health authority. In the United States, these are received and entered into VAERS, which is co-managed by FDA and CDC. In the current pandemic, these reports are being used to monitor the occurrence of both known and unknown adverse events. As part of FDA and CDC's multi-system approach to post-licensure and post-authorization vaccine safety monitoring, VAERS is designed to rapidly detect unusual or unexpected patterns of adverse events. The fact that there has been an increase in reports submitted to VAERS does not alone demonstrate causality, because VAERS is not designed to assess causality. VAERS relies on individuals reporting adverse events after vaccination. Providers of COVID-19 vaccines are required to report SAEs to VAERS, however, anyone can submit reports to VAERS, including vaccine recipients, family members, healthcare providers, and vaccine manufacturers, regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event. Data from VAERS are especially useful for the timely detection of unusual or unexpected patterns of adverse event reporting that might indicate a possible safety concern (or "safety signal") about a vaccine. A certain number of reports of serious illnesses or death, which occur as part of

[90] *Id.*

[91] *See* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adverse-reactions-section-labeling-human-prescription-drug-and-biological-products-content-and. Although the labeling for EUA products is not subject to the regulation in 21 CFR 201.57, for the COVID-19 vaccines FDA has generally applied these principles for labeling of adverse reactions for authorized vaccines.

the usual background rate of these events in the population, do occur by chance alone among persons who have been recently vaccinated, and not due to the vaccine itself. Some of the limitations of VAERS include the lack of an unvaccinated control group - and reports may contain inaccurate or incomplete data. Thus, VAERS is not designed to assess causality. Rather, it is primarily a system for the collection of data, safety signal detection, and hypothesis generation. If VAERS monitoring identifies a potential safety signal, additional scientifically rigorous active surveillance studies or investigations can be conducted by CDC in the Vaccine Safety Datalink (VSD), FDA through its Biologics Effectiveness and Safety (BEST) Initiative[92] and Centers for Medicare & Medicaid Services (CMS) claims data.[93]

We further note that the Petition does not identify any specific adverse reaction information from VAERS, but merely points to the fact that there has been an increase in reports to VAERS. An increase in overall reports cannot provide support for any particular adverse reaction being caused by a vaccine. It is also important to consider factors that have contributed to the volume of VAERS reports. First, we note that a large number of COVID-19 vaccine doses have been administered in the United States and that certain adverse event reporting by vaccination providers is required for all currently authorized COVID-19 vaccines. As of February 09, 2023, over 667,000,000 doses of authorized COVID-19 vaccines have been administered in the United States. 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. Another contributing factor is the v-safe system, which is a CDC smartphone-based active-surveillance system, developed for the COVID-19 vaccination program, in which participants who have been vaccinated may voluntarily enroll. V-safe sends text messages and web surveys to participants who can report side effects following receipt of a COVID-19 vaccine. If a participant indicates through the v-safe surveys that he or she required medical care, CDC calls the participant to complete a report through VAERS. This system is unique to COVID-19 vaccines and may be contributing to the number of VAERS reports submitted for the COVID-19 Vaccines. Finally, an additional potential factor is the concept of "stimulated reporting." Because of extensive media coverage and awareness of the public health emergency—and of COVID-19 vaccines and their reported side effects—vaccine recipients, health care providers, and others may be more likely to report adverse events for the COVID-19 vaccines than for other vaccines that have been widely available for longer periods of time.

[92] FDA, Center for Biologics Evaluation and Research (CBER) Biologics Effectiveness and Safety (BEST) Initiative, https://www.bestinitiative.org/

[93] CMS, Standard Analytical Files (Medicare Claims) – LDS, https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/StandardAnalyticalFiles

For all of these reasons, the fact that there has been an increase in reports to VAERS, in and of itself, does not justify adding the requested adverse reaction information to the labeling.

- The Petition points to a *Lancet* publication[94] to support adding MIS to the Adverse Reactions section of the labeling. However, the *Lancet* publication does not show that there is a causal relationship between vaccination with the Pfizer or Moderna COVID-19 vaccines and MIS in children. As defined in the publication, "multisystem inflammatory syndrome in children (MIS-C), also known as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, is a rare but serious complication of SARS-CoV-2 infection in children and adolescents that generally occurs 2–6 weeks after SARS-CoV-2 infection." The publication examines cases of MIS in children after COVID-19 vaccination which were reported to VAERS and CDC's Clinical Immunization Safety Assessment Project. The authors identified a total of 21 patients meeting the CDC MIS-C case definition, the majority of which (15 of 21) had evidence of past or recent SARS-CoV-2 infection. For those without evidence of prior COVID-19 infection, the reporting rate, based on the number of similarly aged individuals who had received at least one dose of COVID-19 vaccination in the U.S., was 0.3 cases per million vaccinated individuals. The report states that "the contribution of vaccination, if any, to the illnesses in individuals without evidence of infection is unknown and cannot be determined with our surveillance data." The authors additionally explain that some of the 6 individuals without evidence of SARS-CoV-2 infection could have had other had other unrecognized inflammatory conditions [which led to the development of MIS], and/or due to limitations of laboratory assays, some could have had undetected infection with SARS-CoV-2 in the recent past, and vaccination might be coincidental to the subsequent MIS-C illness. Last, given that the pre-pandemic background incidence of illnesses with unidentified diagnosis that would meet the clinical criteria of the MIS-C case definition is unknown, we cannot estimate how often such illnesses would be expected to occur temporally associated with vaccine by chance alone. Considering the small number of reports of MIS-C and the lack of strength of association given the factors stated above, the Petition has not provided sufficient evidence to support a causal relationship between MIS-C in children and vaccination. Therefore, the Petition has not provided evidence that would justify listing MIS-C in children as an adverse reaction in the labeling for the Pfizer and Moderna COVID-19 vaccines.

- The petition cites a *Vaccine*[95] publication as a basis for adding pulmonary embolism to the Adverse Reactions section of the labeling. In the surveillance

[94] Petition at 10 citing: Yousaf *et al*., Reported cases of multisystem inflammatory syndrome in children aged 12–20 years in the USA who received a COVID-19 vaccine, December, 2020, through August, 2021: a surveillance investigation, The Lancet (May 2022), 6(5): 303-12, https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642%2822%2900028-1/fulltext

[95] Petition at 10 citing: Wong *et al*., Surveillance of COVID-19 vaccine safety among elderly persons aged 65 years and older, Vaccine (Jan. 9, 2023), 41(2): 532-39, https://doi.org/10.1016/j.vaccine.2022.11.069

activity described in the publication, FDA and the CMS used data from the Medicare health insurance database to conduct near real-time safety monitoring of 14 outcomes on a weekly basis following COVID-19 vaccine[96] administration. The *Vaccine* publication, authored by FDA scientists, does not show that there is a causal relationship between vaccination with the Pfizer and Moderna COVID-19 vaccines and pulmonary embolism. To the contrary, the publication states that that "[t]his rapid screening method performs hypothesis testing, sequentially, in a prospective manner as the vaccine data accrue to detect potential safety signals earlier in the course of surveillance, but signals must be further evaluated in more robust studies with confounding adjustment," and the publication goes on to state that "results detected by near real-time surveillance do not establish a causal association between the outcomes and vaccination because the method has limited adjustments for confounding [i.e., outside factors that affect the frequency of the outcomes but are unrelated to vaccination]." The results described in the study "should be interpreted cautiously because the early warning system does not prove that vaccines cause the safety outcomes." In addition, the publication states that the "signals are still under investigation and require more robust study." In a July 12, 2021 notice that FDA posted on its website, FDA stated that while the agency had identified pulmonary embolism as a potential adverse event of interest "there are alternative explanations for the findings, including the fact that the Pfizer/BioNTech vaccine was given to many high-risk individuals who were older and had significant co-morbidities." The notice also states that pulmonary embolism, as well other events observed in the near real-time screening, "have not been identified as safety concerns or signals in the CDC Vaccine Safety Datalink (VSD) or the Veterans Administration (VA) Healthcare data systems screening methods."

FDA has subsequently completed two robust studies evaluating the risk of pulmonary embolism among other adverse events following exposure to the primary series and first booster doses of COVID-19 mRNA vaccines in the Medicare population (65 years of age and older). Results of the two studies are publicly available in one manuscript at a pre-print server (at Shoaibi *et al.* 2023) while the manuscript is under peer-review. The incidence rate ratio (IRR) for inpatient pulmonary embolism following BNT162b2 vaccine (Pfizer monovalent COVID-19 vaccine) primary series and first booster doses was 1.19 (95% CI: 1.03 to 1.38) and 0.86 (95% CI: 0.78 to 0.95), respectively; and IRR for mRNA-1273 vaccine (Moderna monovalent COVID-19 vaccine) primary series and booster doses was 1.15 (95% CI: 0.94 to 1.41) and 0.87 (95% CI: 0.79 to 0.96), respectively. The results of these two studies showed that the risk of

[96] The specific COVID-19 vaccines were BNT162b2 (i.e., the Pfizer-BioNTech COVID-19 Vaccine), mRNA-1273 (i.e., the Moderna COVID-19 Vaccine), and Ad26.COV2.S (i.e., the Janssen COVID-19 Vaccine).

pulmonary embolism in the U.S. elderly population following receipt of primary series and first booster doses of COVID-19 mRNA vaccines was not consistent.[97]

- For all of these reasons, the Petition has not provided sufficient evidence to support a causal relationship between pulmonary embolism and vaccination that would justify the requested labeling revision at this time. Therefore, the Petition has not provided evidence that would justify listing pulmonary embolism as an adverse reaction in the labeling for the Pfizer and Moderna COVID-19 vaccines. The Petition points to publication from the Chief Medical Examiner of Connecticut[98] and an autopsy study published in *Clinical Research in Cardiology*[99] as support for adding sudden cardiac death to the Adverse Reactions section of the labeling. In the first of these 2 articles, the authors describe the histologic pathology findings on autopsy in two teenagers who died within one week of receiving the second dose of Pfizer COVID-19 vaccination. Neither individual had complained of fever, chest pain, palpitations, or dyspnea, and neither patient was evaluated or treated for symptoms after vaccination. The authors speculate on a diagnostic association between the histopathologic findings (which they write suggests a catecholamine-induced myocardial injury described as "stress cardiomyopathy" or "neurogenic myocardial injury") and vaccination. They note that these types of syndromes have been observed in individuals with extreme physical, chemical, or emotional stressors. While notable for possible further study, histologic pathology findings in 2 patients, one of whom was obese, is not sufficient to demonstrate a causal association between sudden cardiac death and vaccination. No rates of sudden cardiac death after vaccination, in vaccinated or comparator populations, are presented. Additionally, alternative causes of death, in these cases coronary artery disease, sleep apnea, and any arrhythmogenic substrate, may not be apparent on autopsy.

  In the second paper cited by the petitioner as suggesting evidence of an association between vaccination and sudden cardiac death, the authors reviewed the autopsies of 20 patients who died unexpectedly within 20 days after vaccination and provide detailed histopathologic examination of 5 of them. The authors do not discuss the size of the population from which these patients were selected (i.e., denominator), nor do they, or the petitioner, present the incidence of sudden death in the vaccinated or the general population. The patients included in this series were not characteristic for the patients in whom we usually see myocarditis after vaccination (young men). The youngest patient was 46 with

[97] Shoaibi *et al*., Evaluation of Potential Adverse Events Following COVID-19 mRNA Vaccination Among Adults Aged 65 Years and Older: A Self-Controlled Study in the U.S. medRxiv (Jan. 22, 2023), preprint, doi: https://doi.org/10.1101/2023.01.19.23284803

[98] Petition at 11 citing Gill *et al*., Autopsy Histopathologic Cardiac Findings in 2 Adolescents Following the Second COVID-19 Vaccine Dose, Arch Pathol Lab Med (August 2022) 146 (8): 925–29, https://meridian.allenpress.com/aplm/article/146/8/925/477788/Autopsy-Histopathologic-Cardiac-Findings-in-2

[99] Petition at 11 citing: Schwab *et al*., Autopsy-based histopathological characterization of myocarditis after anti-SARS-CoV-2-vaccination, Clin. Res. Cardiol. (2023), 112: 431–40, https://link.springer.com/article/10.1007/s00392-022-02129-5

concurrent hypertension. The other four patients for whom histopathologic results were provided were all over 50 and two of them had significant co-morbidities. The discussion reviews a common concern regarding the establishment of etiology in autopsy-based studies: the most common cause of sudden death in an older population cohort is coronary artery disease, and the pathology of cardiac ischemia resulting in sudden cardiac death does not develop for 48-72 hours. As a result, an asymptomatic accumulation of histopathologic changes consistent with a benign subclinical myocarditis will appear on autopsy regardless of whether it had a role or not in the patient's demise.

Taken together, these publications show histologic findings in a small number of cases temporally following vaccination, but they do present evidence of an elevated rate of these occurrences associated with vaccination and in some cases alternative etiologies are plausible. Accordingly, the Petition has not provided sufficient evidence to support a causal relationship between sudden cardiac death and vaccination. Therefore, the Petition has not provided evidence that would justify listing sudden cardiac death as an adverse reaction in the labeling for the Pfizer and Moderna COVID-19 vaccines.

- The Petition cites an NIH study (by Safavi *et al*.)[100] and a *Nature Cardiovascular Research* study (by Kwan *et al*.)[101] that the Petition cites as support for adding neuropathic and autonomic disorders to the Adverse Reactions section of the labeling. However, these studies do not demonstrate sufficient evidence to add these conditions to the labeling.

  The Safavi *et al*. manuscript, a preprint which has not yet been peer reviewed by a journal, describes a case series of patients with diverse signs, symptoms, and laboratory findings, who received a COVID-19 vaccine within 21 days of symptom onset. The patients did not share many clinical characteristics, but rather there was a wide range of clinical presentations, with some clusters of similar symptoms. As the paper's authors note their data is limited by referral bias. They also state that although the symptoms are temporally associated with vaccination, they cannot attribute causation to the COVID-19 vaccines, because the study is uncontrolled. As such, this unpublished manuscript does not demonstrate sufficient evidence to support a causal relationship between vaccination and "neuropathic and autonomic disorders."

  In the paper by Kwan *et al.*, the authors performed a sequence-symmetry analysis, comparing the 90 days prior to the COVID-19 vaccine to 90 days following the COVID-19 vaccine. They found the post-vaccination odds of new POTS-associated diagnoses was higher than common primary care diagnoses which was

[100] Petition at 11 citing: Safavi *et al*., Neuropathic symptoms with SARS-CoV-2 vaccination, medRxiv (May 17, 2022), preprint: 2022.05.16.22274439, https://pubmed.ncbi.nlm.nih.gov/35611338/

[101] Petition at 11 citing: Kwan *et al*., Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 Infection, Nature Cardiovascular Research (2022), 1: 1187–94, https://www.nature.com/articles/s44161-022-00177-8

used as the control. This study had some limitations. The authors did not formally adjudicate all diagnoses due to the large number of events. The diagnostic criteria for POTS require symptoms to occur over a duration of at least 3 months which was the same length as the assessment period of the study. As the author's state this could have led to an overestimation the incidence of POTS and POTS-associated diagnoses. The authors go on to state that due to the observational design of the study, the results "should not be interpreted as definitive for any causal links between COVID-19 vaccination and POTS." This study therefore also fails to demonstrate any causal relationship between vaccination and "neuropathic and autonomic disorders."

In summary, the manuscript by Safavi *et al*. (not yet peer reviewed by a journal) and the Kwan *et al*. peer reviewed publication, do not sufficiently demonstrate that there is a reason to believe there is a causal association between the vaccine and the event "neuropathic and autonomic disorders." The Petition therefore fails to provide evidence that would justify the requested labeling change.

Thus, the scientific sources cited in the Petition do not provide a basis for the requested actions. As an additional matter, FDA's own safety monitoring does not support the requests. To date, the Agency's systems for monitoring COVID-19 vaccine safety have not identified evidence that provides a sufficient basis to believe that there is a causal relationship between these outcomes and the use of the Pfizer and Moderna COVID-19 vaccines that would justify the labeling revisions. Therefore, at this time FDA is not aware of sufficient information about MIS in children, pulmonary embolism, sudden cardiac death, and neuropathic and autonomic disorders to support adding these events to the Adverse Reactions section of the labeling for the Pfizer and Moderna COVID-19 vaccines, and the Petition has not provided such information. These requests are denied. FDA will continue to closely monitor reports of all adverse events and will consider labeling changes as warranted.[102]

H. Petitioner's Request That FDA Amend Current Labeling to Add Additional Adverse Reactions Relating to Reproductive Health and Lactation

- **i.** Decreased sperm concentration
- **ii.** Heavy menstrual bleeding
- **iii.** Detection of vaccine mRNA in breastmilk

The Petition states that "[t]he following reproductive health and lactation related adverse event types should be added to the Adverse Reactions section of labeling:" decreased sperm concentration ("Pfizer only"); heavy menstrual bleeding; and detection of vaccine mRNA in breastmilk.

[102] The Petition devotes a paragraph to describing FDA's analysis of the risk of thrombosis with thrombocytopenia syndrome (TTS) associated with the Janssen COVID-19 Vaccine. However, the Petition does not explain why FDA's actions with respect to the TTS risk of the Janssen COVID-19 Vaccine provide a basis for the Petition's requested actions. For more information about FDA's analysis of the TTS risk of the Janssen COVID-19 Vaccine, see FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum, (May 5, 2022), https://www.fda.gov/media/158318/download.

In support of this request, the Petition cites to several scientific sources. However, the Petition fails to support the requested actions. Specifically:

With respect to the request to add decreased sperm concentration to the Adverse Reactions section of the labeling, the Petition cites to a postmarketing study of sperm donors who had received Pfizer vaccine in Israel. Published in *Andrology*[103], the Petition describes the study as having "found that vaccination temporarily impairs semen concentration and total motile count among semen donors." However, the study was not of the quality that would allow the agency to draw scientific conclusions because of the methodological deficiencies of the study including small sample size, lack of comparator, lack of correction for multiple comparisons, and different composition of samples at each time point. As an additional matter, the study concluded that the findings were "transient" and "[l]ong-term prognosis remains good." The authors state that "the retrospective design and inclusion of sperm donors necessitate further research."[104] Additional studies have explored the issue of the interaction between COVID-19 vaccines and spermatogenesis and multiple studies have shown no decrease in sperm counts[105] [106] during the comparable time period of the Gat *et al*. study, or long term.[107] All the studies cited, including those cited in the petition, have relatively small cohorts, and although they do not definitively exclude an interaction between COVID-19 vaccination and sperm counts, there is not sufficient evidence of a causal relationship between vaccination and decrease in sperm counts that would justify listing this outcome as an adverse reaction in labeling for the Pfizer and Moderna COVID-19 vaccines.

With respect to the request to add heavy menstrual bleeding, the Petition cites to the European Medicine Agency's decision to add this side effect to the vaccines and a study published in *BMJ Medicine.*[108] The BMJ Medicine publication did not evaluate heavy menstrual bleeding but rather found some evidence of transient changes in menstrual cycle length that are not likely clinically significant. Thus, this article does not support the request to add heavy menstrual bleeding to the products' labeling. While some international regulatory agencies have added this as a potential side effect to the package information for the Moderna and Pfizer COVID-19 vaccines, foreign regulatory agencies' expectations and regulations regarding product labeling can differ from those of the U.S. FDA. At this time, FDA has not identified evidence that provides a basis to believe there is a causal relationship between COVID-19 vaccines and heavy

---

[103] Petition at 13 citing: Gat *et al*., Covid-19 vaccination BNT162b2 temporarily impairs semen concentration and total motile count among semen donors, Andrology (September 2022), 10(6): 1016-22, https://doi.org/10.1111/andr.13209

[104] Gat *et al*.,. Response to: There is not enough evidence to support the claim that Covid-19 vaccination BNT162b2 temporarily impairs semen concentration and total motile count. Andrology. (January 11, 2023), 11(1):8-9, doi: 10.1111/andr.13313. (Epub: November 21, 2022)..

[105] Gonzalez, *et al*., Sperm Parameters Before and After COVID-19 mRNA Vaccination, JAMA. (July 20, 2021),326(3): 273-274. doi: 10.1001/jama.2021.9976.

[106] Massarotti *et al*., mRNA and Viral Vector COVID-19 Vaccines Do Not Affect Male Fertility: A Prospective Study, World J Mens Health. (October 2022),40(4): 561-69, doi: 10.5534/wjmh.220055. (Epub: August 16, 2022.

[107] Karavani *et al*., Sperm quality is not affected by the BNT162b2 mRNA SARS-CoV-2 vaccine: results of a 6-14 months follow-up, J Assist Reprod Genet (October 2022), 39(10): 2249-54, doi: 10.1007/s10815-022-02621-x. (Epub: September 17, 2022).

[108] Petition at 13 citing: Edelman *et al*., Association between menstrual cycle length and covid-19 vaccination: global, retrospective cohort study of prospectively collected data, BMJ Medicine (2022), 1: e000297, https://doi.org/10.1136/bmjmed-2022-000297.

menstrual bleeding, and the Petition does not set forth an adequate basis for listing heavy menstrual bleeding as an adverse reaction in the labeling for the Pfizer and Moderna COVID-19 vaccines. The agency will continue to monitor for potential adverse reactions of the authorized and approved COVID-19 vaccines and will consider labeling changes as warranted.

To support the request to add information to the Adverse Reactions section regarding the detection of mRNA in breastmilk, the Petition cites a study published in *JAMA Pediatrics*.[109] The Petition cites the publication for the proposition that "the presence of vaccine mRNA in breast milk for at least 48 hours after maternal vaccination" has been documented. However, the Petition fails to explain why the detection of mRNA described in the publication is a basis for adding information to the Adverse Reactions section. The publication describes findings demonstrating only "sporadic presence and trace quantities" of mRNA in breastmilk, and "suggest that breastfeeding after COVID-19 mRNA vaccination is safe, particularly beyond 48 hours after vaccination." The authors also acknowledge that the study includes a "relatively small sample size" (11 subjects) and state that the study findings are limited by a "lack of functional studies demonstrating whether detected vaccine mRNA is translationally active." These findings are not sufficient evidence to demonstrate that any effects of mRNA constitute an "undesirable effect" such that detection of mRNA in breast milk would be considered an adverse reaction.[110] The Petition therefore has not provided evidence to justify listing the presence of mRNA as an adverse reaction in the labeling for the Pfizer and Moderna COVID-19 vaccines.

Thus, the scientific sources cited in the Petition do not provide a basis for the requested actions. As an additional matter, FDA's own safety monitoring does not support the requests. To date, the Agency's systems for monitoring COVID-19 vaccine safety have not identified evidence that provides a sufficient basis to believe that there is a causal relationship between these outcomes and the use of the Pfizer and Moderna COVID-19 vaccines. Therefore, at this time FDA is not aware of sufficient information about decreased sperm count, heavy menstrual bleeding, or mRNA in breastmilk to support adding these events to the Adverse Reactions section of the labeling for the Pfizer and Moderna COVID-19 vaccines, and the Petition has not provided such information. These requests are denied. FDA will continue to closely monitor reports of all adverse events and will consider labeling changes as warranted.

I. Petitioner's Request That FDA Amend Current Labeling to Add Frequency Data for Clinical and Subclinical Myocarditis

The Petition makes the following request: "[a]dd frequency data for clinical and subclinical[111] myocarditis."

---

[109] Petition at 14 citing: Hanna *et al*., Detection of Messenger RNA COVID-19 Vaccines in Human Breast Milk, JAMA Pediatr. (2022), 176(12): 1268-70, https://jamanetwork.com/journals/jamapediatrics/fullarticle/2796427.
[110] 21 CFR 201.57(c)(7).
[111] Although the Petition refers to subclinical myocarditis, the Petition's explanation for this request does not refer to subclinical myocarditis – but rather refers to myocarditis generally. Therefore, we focus our response on myocarditis generally.

While the Petition acknowledges that the labeling of the Pfizer and Moderna COVID-19 vaccines includes adverse reaction information about the risks of myocarditis and pericarditis, the Petition requests that FDA update the labeling to include information about the *frequency* of these adverse events. The Petition asserts that "Labels should contain a range of rates that have been reported in the literature, and should stratify estimates by risk factors (notably, age and sex)." Although the Petition does not propose specific rates or risk factors to be included in the labeling, the Petition cites to three studies for the purpose of characterizing these risks.

Data on myocarditis and pericarditis have accrued with use of these vaccines and as soon as FDA became aware of the risks and determined that there was reasonable evidence of a causal association with the mRNA COVID-19 vaccines, a Warning was included in the Fact Sheets. As additional post-marketing data accrues over time, we continue to evaluate the data and assess the robustness and the quality of the data to determine whether updates to the labeling are warranted. Over time, based on the data that has accrued, the Warning in the Fact Sheets has been updated to strengthen it and to include language to convey information about risk factors (i.e., risk information based on age and sex).

The Petition does not take issue with FDA's actions to add myocarditis and pericarditis information to the labeling, but instead requests that the labeling be revised to include information about frequency of these risks. The Petition's request therefore implicates the question of when frequency information about adverse reactions should be included in labeling. Within the Adverse Reactions section in prescription drug labeling for approved drugs and biological products, our regulation provides that "the frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed[.]"[112] Although the Petition identifies three studies that intend to characterize myocarditis and pericarditis risks, the Petition does not provide any explanation as to why frequency information is necessary for the safe and effective use of the Pfizer and Moderna COVID-19 vaccines.

At this time, based on the information available to us, we do not believe that it is necessary for the labeling of the Pfizer and Moderna COVID-19 vaccines to include frequency information about myocarditis and pericarditis risks in order to ensure the safe and effective use of the vaccines, and the Petition has not provided any explanation as to why such labeling information is necessary. The existing labeling already includes detailed information about these risks that accurately conveys relevant safety information. For example, the Warnings and Precautions section of the Comirnaty package insert states that "[p]ostmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose." The package insert then goes on to state that "[t]he observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 12 through 17 years of age."[113] For the healthcare provider Fact Sheet for the Moderna COVID-19 Vaccine, Bivalent, the Warnings and Precautions section of the Fact Sheet includes similar information. It states that "[p]ostmarketing data with authorized or approved monovalent mRNA COVID-19 vaccines demonstrate increased risks of myocarditis and pericarditis, particularly

[112] 21 CFR 201.57(c)(6)(i).
[113] See Comirnaty package insert, *available at* https://www.fda.gov/media/154834/download

within the first week following vaccination."[114] The Fact Sheet also states, "[f]or Moderna COVID-19 Vaccine,[115] the observed risk is highest in males 18 through 24 years of age." Given the information already provided in the labeling, including about demographic groups for whom the observed risk is most significant, we do not believe that additional information about frequency is needed to ensure the safe and effective use of the vaccines at this time. Going forward, we will continue to evaluate the myocarditis and pericarditis risks as new information becomes available. We anticipate that any determinations for additional updates to the labeling will be primarily based on data from VSD and BEST (two large, U.S.-based active surveillance systems) and the required post-marketing studies being conducted by the manufacturers.

J. Petitioner's Request That FDA Amend Current Labeling to Add Serious Adverse Events in Tables with Statistics

The Petition requests that "[l]abeling should present trial results on serious adverse events in tables with statistics[.]"[116] The Petition states that this is done in the labeling for non-serious adverse events, and that the lack of a tabular format for serious adverse events "prevents easy understanding of risk."[117]

For purposes of prescription drug labeling, FDA generally considers serious adverse reactions (SAEs) to refer to any reaction occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect.[118]Within a listing of adverse reactions in prescription drug labeling for approved products based on clinical trial experience, this section of the labeling must list the adverse reactions identified in clinical trials and must include the rate of occurrence of an adverse reaction for the drug and any comparators (active- or placebo-controls), unless such data cannot be determined or presenting the rates for a comparator would be misleading.[119] To permit side-by-side comparison of adverse reaction rates, common adverse reactions are typically presented in a table.[120] A table can include less common, even rare, important events when the database is large enough to provide a meaningful comparison to a control group.[121]

However, a table format is not required nor is it always the best option. A table format may not always be the optimal communications tool, for example when there is not enough data to show comparisons. For the Pfizer and Moderna COVID-19 vaccine labeling, the SAEs are presented, but not via a table format. The information is conveyed using clear and easy-to-understand

---

[114] See Moderna COVID-19 Fact Sheets for Healthcare Providers Administering Vaccine (Vaccination Providers), *available at* https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccines#additional

[115] *Id.* The Fact Sheet explains that postmarketing safety data with Moderna COVID-19 Vaccine are relevant to the Moderna COVID-19 Vaccine, Bivalent because these vaccines are manufactured using the same process.

[116] Petition at 15.

[117] *Id.*

[118] *See* January 2006 Adverse Reactions Section of Labeling Guidance.

[119] *See* January 2006 Adverse Reactions Section Labeling Guidance; and 21 CFR 201.57(c)(7)(ii)(A).

[120] January 2006 Adverse Reactions Section Labeling Guidance.

[121] *Id.*

language. The Petition asserts that the lack of a tabular format "prevents easy understanding of risk," but fails to explain why this is so. The Petition provides no information explaining why the format for presenting the SAE information causes the labeling to be inaccurate, false, or misleading, or why the format for presenting the SAE information causes the labeling to be otherwise in violation of FDA's statutes or regulations. The Petition therefore does not provide an adequate basis for the requested action, and we thus deny the request.

K. Petitioner's Request That FDA Create a Medication Guide

The Petition also requests the FDA create a Medication Guide.[122] The Petition provides no explanation for this request.

Section 208.1(c) states that a Medication Guide will be required if FDA determines one or more of the following circumstances exist:

> (1) The drug product is one for which patient labeling could help prevent serious adverse effects.
>
> (2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.
>
> (3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness."[123]

The Petition has not shown that any of these circumstances exist for the Pfizer and Moderna COVID-19 vaccines. Therefore, the Petition has not provided a basis for the request to create a Medication Guide. Accordingly, we deny the request.

L. Petition's Request to Create a Dear Healthcare Provider Letter to "communicate these labeling changes"

The Petition requests that FDA create a Dear Healthcare Provider Letter to "communicate these labeling changes," but does not otherwise explain this request.[124]

A Dear Healthcare Provider letter is "used to notify health care providers about important new or updated information about a drug. In most cases, the information relates to an important safety

---

[122] Petition at 1.

[123] 21 CFR 208.1(c).

[124] The Petition also does not make clear what "these labeling changes" refers to. The request appears in a sentence about the Medication Guide request, so it is possible that the request is asking for a Dear Healthcare Provider Letter addressing a Medication Guide. On the other hand, it is also possible that the request is asking for a Dear Healthcare Provider letter addressing all of the labeling revisions requested in the Petition. In any case, the main text explains why we deny the request. Irrespective of whether the Dear Healthcare Provider Letter is intended to be narrow (and refer only to a Medication Guide labeling change) or broad (and refer to all of the Petition's requested labeling changes), the Petition fails to justify the request for a Dear Healthcare Provider letter.

concern that could affect the decision to use a drug or require some change in behavior by health care providers, patients, or caregivers to reduce the potential for harm from a drug."[125]

As part of today's action revising the EUAs for the bivalent Pfizer and Moderna COVID-19 vaccines, Moderna is issuing a Dear Healthcare Provider letter that explains how two of the vial presentations for the vaccine are to be used. However, the Dear Healthcare Provider Letter does not explain the labeling changes requested in the Petition. The only labeling change request in the Petition that we are granting (regarding providing certain updated clinical data on the Pfizer-BioNTech COVID-19 Vaccine, Bivalent) is not the type of information that would be consistent with the purpose of a Dear Healthcare Provider letter. That labeling change does not relate to important safety concerns that could affect the decision to use the vaccine. Nor does that data, in and of itself, require any change in behavior by healthcare providers, vaccine recipients, or caregivers. Furthermore, the Petition provides no explanation for why the labeling changes requested in the Petition merit a Dear Healthcare Provider letter. For these reasons, we deny the request.

IV. CONCLUSION

We grant the request regarding describing certain data related to the Pfizer-BioNTech COVID-19 Vaccine, Bivalent. For the reasons given above, FDA denies all other requests.

Sincerely yours,

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

cc: Dockets Management Staff

[125] Dear Healthcare Provider Letters: Improving Communication of Important Safety Information, Guidance for Industry and FDA Staff, January 2014, Three types of Dear Healthcare Provider Letters are described in FDA's regulations. One, which "concerns a significant hazard to health," is described in 21 CFR 200.5(c)(1). Important Prescribing Information Letters are described in 21 CFR 200.5(c)(2). Finally, Important Correction of Drug Information letters are described in 21 CFR 200.5(c)(3).