January 31, 2023

Electronic Submission

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

This petition for administrative action is submitted on behalf of CAALM, the Coalition Advocating for Adequately Labeled Medicines ("Petitioner"), pursuant to 21 C.F.R. § 10.30 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, to request that the Commissioner of Food and Drugs (the "Commissioner") 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.

Incomplete, inaccurate, or misleading labeling of any medical product can negatively impact the health and safety of Americans, with global ramifications considering the international importance of FDA decisions. For these reasons, and due to the compelling need to ensure the safety and efficacy of any COVID-19 vaccine licensed by the FDA and to allow Petitioner the opportunity to seek emergency judicial relief should the instant Petition be denied, it is respectfully requested that FDA act on the instant Petition by April 30, 2023.

I. ACTIONS REQUESTED

Petitioner requests that the FDA amend current labeling[i] of Pfizer and Moderna COVID-19 vaccines (for all authorized or approved indications and populations) in the following ways:

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.

[i] Labeling includes all Package Inserts (Pfizer & Moderna), all EUA Fact Sheets for Vaccination Providers (Pfizer, Moderna), and, as appropriate, all patient oriented materials such as EUA Fact Sheets for Recipients and Caregivers (Pfizer, Moderna) and Patient Package Inserts (Moderna).[1–9]

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;
    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.

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

II. STATEMENT OF GROUNDS

Here, in the order as above, we set out the rationale for each requested action.

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.

In December 2020, when Emergency Use Authorizations (EUAs) were granted, FDA made clear that the clinical trials were not designed to evaluate--and data collected did not demonstrate--an effect against SARS-CoV-2 transmission.[10,11]

Below is the wording from the FDA EUA review memo[10] (the same statements are made for Moderna vaccine[11]):

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine against asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[12-15] Benefits in preventing death should be evaluated in large observational studies following authorization.

FDA EUA memo pp.50-51 (Dec 1, 2020)[10]

Months later, FDA's evaluation remained the same: efficacy against transmission remained unproven:

against hospitalization and death appears stable at this time. Remaining uncertainties regarding the clinical benefits of BNT162b2 in individuals 16 years and older include its level of protection against asymptomatic infection and transmission of SARS-CoV-2, including for the delta variant, durability of protection beyond 6-8 months (the current

FDA clinical review memo, p.98 (Aug 23, 2021)[12]

Today, FDA remains clear that efficacy against transmission is unproven. For Pfizer and Moderna vaccines,[13,14] the FDA states:

A: Most vaccines that protect from viral illnesses also reduce transmission of the virus that causes the disease by those who are vaccinated. While it is hoped this will be the case, the scientific community does not yet know if the Pfizer-BioNTech COVID-19 Vaccine will reduce such transmission.

FDA "Pfizer-BioNTech COVID-19 Vaccine Frequently Asked Questions" (2023)[13]

While language in labeling that states what a product has not been proven to do is uncommon, it is necessary when caregivers and patients may inaccurately assume something that is untrue. For example, in 2000, Roche promotional materials stated that oseltamivir (Tamiflu) "reduces incidence of secondary complications (ie bacterial infections) by 45%" (an important pandemic

planning assumption).[15] FDA warned Roche that this was a "misleading efficacy claim" that was "not supported by substantial evidence."[16] Subsequently, product labeling (*Warnings and Precautions* section) was amended to state that "Tamiflu has not been shown" (emphasis added) to prevent serious complications of influenza.

5.3 Risk of Bacterial Infections

There is no evidence for efficacy of TAMIFLU in any illness caused by pathogens other than influenza viruses. 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.
Prescribers should be alert to the potential for secondary bacterial infections and treat them as appropriate.

Current FDA-approved TAMIFLU label (p.9)[17]

The situation is similar for Pfizer and Moderna vaccines. There 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. Inaccurate statements to this effect have been made by the U.S. President,[18] CDC Director,[19] and former Director of the NIAID,[20] and are directly implied in statements by FDA,[21] Pfizer,[22] and Moderna,[23] suggesting that widespread uptake of these vaccines would result in herd immunity.

President Biden 7/21/21: "you're not going to get COVID if you have these vaccinations."[18]

Dr. Anthony Fauci 5/16/21: "when you get vaccinated, you not only protect your own health … you become a dead end to the virus."[20]

Dr. Rochelle Walensky 3/29/21: "vaccinated people do not carry the virus, don't get sick, and that it's not just in the clinical trials but it's also in real world data."[19]

FDA 8/23/21: "Public health vaccination goals of immunizing 75% of the population (to achieve herd immunity) have not yet been achieved."[12]

Pfizer 10/26/21: "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."[24]

Moderna (2021-2023): "To safely achieve herd immunity against COVID-19, a large amount of a population needs to be vaccinated."[23]

To remedy this situation, 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 must be added to labels.[ii]

[ii] Also see FDA labeling requirements (21CFR201.57) which states: "If 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, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition."

2. Add language clarifying that the immunobridging surrogate endpoint used in multiple authorized indications has not been validated to predict clinical efficacy.

According to FDA's labeling requirements (21CFR201.57), drugs approved based on a surrogate endpoint must include "a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits."

FDA has granted multiple EUAs on the basis of trials that used an immunobridging primary efficacy endpoint (neutralizing antibody titers)--e.g., Pfizer EUAs for: 6 months to 4 year olds (see FDA memo p.6), 5 to 11 year olds (see FDA memo p.4), 12 to 15 year olds (see FDA memo p.5), booster #1 (see FDA memo p.4), booster #2 (see FDA memo p.2); and Moderna EUAs for 6 months to 17 year olds (see FDA memo p.10), booster #1 (see FDA memo p.6), and booster #2 (see FDA memo p.2).[25–32]

This immunobridging surrogate endpoint has not been validated to predict clinical efficacy.

Pfizer acknowledged this in 2021, at the first Advisory Committee meeting to discuss the first booster dose (dose 3), stating that it had not ascertained a correlate of protection (see figure).

DR. KATHRIN JANSEN: German technology. I'm just kidding. I just wanted to say that we actually looked in our breakthrough cases in our placebo-controlled phase III study and have compared the antibody titers where we had the opportunity in individuals who got the disease versus the ones that didn't. And we were also unable to really come up with an antibody threshold. So I think it's probably a much more complex story and not just easily addressed with neutralizing antibodies. Thank you.

DR. JAMES HILDRETH: Thank you.

DR. ARNOLD MONTO: That sounds reasonable.

FDA advisory committee meeting transcript, p.243 (September 17, 2021)[33]

FDA confirmed the lack of a validated surrogate endpoint in an April 2022 advisory committee meeting:

> *"There is not a clear, perfect, immune correlate of protection, and so we're using poor man's immune correlates of protection here -- or poor person's immune correlates of protection with antibody levels."*[34]

FDA reiterated those concerns in a December 2022 *JAMA* commentary stressing the "Urgent Need for Next-Generation COVID-19 Vaccines":

> *"Therefore, unless correlates of protection that are strongly associated with duration of protection against COVID-19 can be identified, it is likely that rather than relying on immunobridging to infer vaccine effectiveness, large randomized clinical trials similar to the initial trials of the currently authorized or licensed vaccines for COVID-19 will be required to ascertain the effectiveness of these new vaccines."*[35]

While 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 21CFR201.57. Labeling should be updated to reflect this.

3. Add safety and efficacy results data from manufacturer randomized trials of current bivalent boosters that reported results after EUA was granted.

On August 31, 2022, FDA granted Pfizer and Moderna EUAs for Bivalent (Original and Omicron BA.4/BA.5) vaccines.[36,37] These authorizations were granted despite the fact that the new vaccine formulations had not completed any human testing.

> While clinical data for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) are not yet available, FDA determined that for purposes of this EUA it is reasonable to assess the effectiveness and the known and potential benefits and risks of this bivalent vaccine based primarily on extrapolation of data from another bivalent vaccine, Bivalent BA.1, manufactured by the same process and containing original and Omicron BA.1 components, and extensive experience to date with the original Pfizer-BioNTech COVID-19 Vaccine. This

FDA Decision Memo p.5 (Aug 31, 2022)[36]
Identical wording for Moderna in FDA Decision Memo, p.6 (Aug 31, 2022)[37]

After the EUA was granted, in November 2022, Pfizer and Moderna both reported results in press releases of Phase 2/3 randomized trials of Bivalent (Original and Omicron BA.4/BA.5) boosters (NCT05472038 and NCT04927065).[38,39]

At 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;[40,41] labeling should be updated to reflect current data.

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.

Vaccine safety and efficacy data provided in labeling[iii] for children 6 months to 4 years of age and 5 to 11 years of age are based on Pfizer study C4591007 (NCT04816643),[4,5] and data for

[iii] Efficacy data from trials is presented in section 18 in Fact Sheets and section 14 in Package Inserts. Safety data from trials is provided in section 6 in Fact Sheets section 6.1 in Package Inserts.

ages 16 years and older are based on Pfizer study C4591001 (NCT04368728) and BioNTech trial BNT162-01 (NCT04380701).[1]

However, these trials all studied a formulation of the vaccine that differs from three of the four FDA authorized or approved formulations.

Specifically, these clinical trials all used a vaccine formulation containing a phosphate (PBS) buffer. However, the "gray cap," "maroon cap", and "orange cap" formulations in use contain a tromethamine (Tris) buffer.[1,4,5]

The Pfizer vaccine containing a Tris buffer was first authorized in October 2021, for the EUA for 5 to 11 year olds. The FDA decision memo noted that the authorized vaccine was for a new formulation "containing tromethamine (Tris)/Sucrose buffer instead of the phosphate-buffered saline (PBS)/Sucrose buffer as used in the previous formulation."[26] No clinical trials were conducted to evaluate the efficacy, safety, or bioequivalence of the new product; only laboratory assessments were conducted.

Therefore, a clear statement should be added to labeling stating that the authorized or approved indications containing a Tris buffer is for a formulation that was not studied in these trials.

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.

Pregnant women were excluded from the original clinical trials.[42,43] In June 2021, a *New England Journal of Medicine* editorial[44] discussed the urgent need for trials in this population:

> *"The dearth of safety information about pregnancy, which existed at a time when thousands of pregnant women were grappling with decisions about vaccination, highlights the importance of recent efforts to enroll pregnant women in trials, including ongoing vaccine trials; a trial is currently under way to study the effects of the BNT162b2 vaccine in pregnant women and their infants (ClinicalTrials.gov number, NCT04754594)"*[44]

This Pfizer trial of pregnant women began in February 2021 (NCT04754594), but before results were available, the CDC and professional societies such as the American Congress of Obstetricians and Gynecologists (ACOG) recommended all pregnant women get vaccinated.[45,46] The trial originally intended to enroll 4,000 women, but enrollment was inexplicably stopped in Q4 2021 with just 349 participants.

One year later, nothing has appeared in the literature: no publication, no preprint, no conference abstract.

Section 8.1 Pregnancy of current labeling discusses animal data, but omits mention that the existing trial in pregnant women has not yet reported results. This should be noted on the label. Once FDA receives the pregnancy trial data, results should be added to the label.

6. Add a clear statement that Pfizer vaccine efficacy wanes after 2 months following dose 2 according to the Pfizer phase III randomized trial.

Current 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.

An internal Pfizer report[47] shows that these results were available in April 2021, but they were not publicly disclosed until July 2021, in a Pfizer preprint.[48]

> In this same all-available (modified intention-to-treat) population, the estimated VE against all cases occurring ≥7 days after Dose 2 was 91.2%. The estimated VE was 91.7% from ≥11 days after Dose 1 to before Dose 2, 96.2% for cases occurring from ≥7 days after Dose 2 to <2 months after Dose 2, 90.1% for the period from ≥2 months to <4 months after Dose 2, and 83.7% for the period ≥4 months after Dose 2.

Pfizer Interim 6-Month Report Body p.120 (April 29, 2021)[47]

Table 18. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Blinded Placebo-Controlled Follow-up Period – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=23040)		Placebo (N[a]=23037)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	131	8.412 (22505)	1034	8.124 (22434)	87.8	(85.3, 89.9)
After Dose 1 to before Dose 2	46	1.339 (22505)	110	1.331 (22434)	58.4	(40.8, 71.2)
After Dose 1 to <11 days after Dose 1	41	0.677 (22505)	50	0.675 (22434)	18.2	(-26.1, 47.3)
≥11 Days after Dose 1 to before Dose 2	5	0.662 (22399)	60	0.656 (22369)	91.7	(79.6, 97.4)
Dose 2 to 7 days after Dose 2	3	0.424 (22163)	35	0.422 (22057)	91.5	(72.9, 98.3)
≥7 Days after Dose 2	82	6.649 (22132)	889	6.371 (22001)	91.2	(88.9, 93.0)
≥7 days after Dose 2 to <2 Months after Dose 2	12	2.923 (22132)	312	2.884 (22001)	96.2	(93.3, 98.1)
≥2 Months after Dose 2 to <4 Months after Dose 2	46	2.696 (20814)	449	2.593 (20344)	90.1	(86.6, 92.9)
≥4 Months after Dose 2	24	1.030 (12670)	128	0.895 (11802)	83.7	(74.7, 89.9)

Abbreviation: VE = vaccine efficacy.

Pfizer Interim 6-Month Report Body p.102 (April 29, 2021)[47]

7. The following adverse event types should be added to the Adverse Reactions section of labeling:

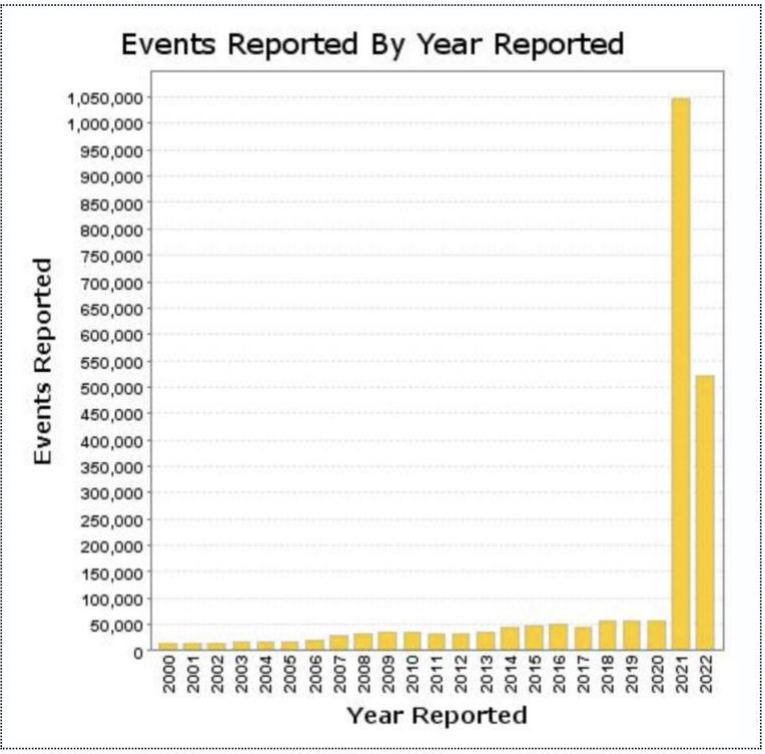
- **multisystem inflammatory syndrome (MIS) in children;**
- **pulmonary embolism** [Pfizer only];
- **sudden cardiac death;**
- **neuropathic and autonomic disorders.**

Since the introduction of COVID-19 vaccines, there has been a dramatic increase in reports to the Vaccine Adverse Event Report System (VAERS).

The volume of reports has coincided with an increase in published postmarketing safety studies.

A causal relationship does not need to be established before adding adverse events to the label that are detected in the postmarketing period. In fact, *Section 6.2 Postmarketing Experience* of the label already states that "Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure."[1,3]

The type, quality, and amount of evidence needed to justify adding a new adverse event type to labeling is not specified in FDA guidance. In the case of Janssen (J&J) COVID-19 vaccine, on April 13, 2021 the vaccine was "paused" pending the review of 6 cases of cerebral venous sinus thrombosis (CVST) with thrombocytopenia.[49] (All six reports came from VAERS; CDC's electronic health record real-time surveillance system Vaccine Safety Datalink did not detect a signal.[50]) Ten days later, product labeling was amended to include a warning regarding this syndrome with a total of 15 confirmed cases of Thrombosis with Thrombocytopenia Syndrome (TTS) discovered within VAERS.[51]



CDC Wonder search on VAERS. Data current as of January 13, 2023
https://wonder.cdc.gov/controller/saved/D8/D321F831

Multisystem inflammatory syndrome in children should be added to *Section 6.2 Postmarketing Experience* of the label.

A CDC and FDA authored study published in *Lancet Child & Adolescent Health* identified 6 children, through August 31, 2021, who suffered multisystem inflammatory syndrome (MIS) following COVID-19 vaccination who were without evidence of SARS-CoV-2 infection, had no alternative diagnosis, and no previous history of MIS-C.[52] (See Figure.)

The CDC and FDA authors called for enhanced pharmacovigilance:

> *"Continued surveillance for MIS-C illness after COVID-19 vaccination is warranted, especially as paediatric COVID-19 vaccination is authorised for younger children, who comprise the highest proportion of MIS-C cases after SARS-CoV-2 infection. US providers are encouraged to report potential MIS-C cases after COVID-19 vaccination to VAERS."*[52]

* * *

	Total	Onset after first dose of COVID-19 vaccine	Onset after second dose of COVID-19 vaccine
MIS-C	21	11 (52%)	10 (48%)
With evidence of SARS-CoV-2 infection	15	10 (67%)	5 (33%)
Positive NAAT (past or recent)*	10	5 (50%)	5 (50%)
Negative NAAT and positive anti-nucleocapsid antibody test	5	4 (80%)	1 (20%)
Without evidence of SARS-CoV-2 infection†	6	1 (17%)	5 (83%)

Data are n or n (%). MIS-C=multisystem inflammatory syndrome in children. NAAT=nucleic acid amplification test. *Includes five individuals with positive SARS-CoV-2 NAAT before MIS-C illness, four with positive SARS-CoV-2 NAAT during MIS-C illness, and one with a positive SARS-CoV-2 NAAT before and during MIS-C illness. †Negative NAAT, negative anti-nucleocapsid antibody test, and positive anti-spike antibody test during MIS-C illness evaluation; these individuals did not have any reported positive NAAT results before MIS-C illness.

Table 2: **SARS-CoV-2 laboratory testing in 21 individuals with MIS-C who had received a COVID-19 vaccine**

Pulmonary embolism should be added to *Section 6.2 Postmarketing Experience* of Pfizer vaccine labeling.

An FDA-authored postmarketing study published in *Vaccine* detected a signal for this serious adverse event.[53]

> *Findings:* Four outcomes met the threshold for a statistical signal following BNT162b2 vaccination including pulmonary embolism (PE; RR = 1.54), acute myocardial infarction (AMI; RR = 1.42), disseminated intravascular coagulation (DIC; RR = 1.91), and immune thrombocytopenia (ITP; RR = 1.44). After further evaluation, only the RR for PE still met the statistical threshold for a signal; however, the RRs for AMI, DIC, and ITP no longer did. No statistical signals were identified following vaccination with either the mRNA-1273 or Ad26 COV2.S vaccines.

FDA study (Wong et al. 2022)[53]

Although these findings were made between February and April 2021, they have not yet been added to product labeling.

* * *

Sudden cardiac death should be added to *Section 6.2 Postmarketing Experience* of the label.

Multiple autopsy-based published studies have reported on lethal vaccination-associated myocarditis.[54–57] In one paper, the Chief Medical Examiner of Connecticut and colleagues published on 2 adolescents who died following the second dose of Pfizer vaccine, finding "features resembling a catecholamine-induced injury, not typical myocarditis pathology."[56] In another autopsy study published in *Clinical Research in Cardiology*, researchers reported on all autopsies (n=35) performed at the Institute of Pathology, Heidelberg University Hospital in which death occurred within 20 days of COVID-19 vaccination. mRNA vaccines (Pfizer and Moderna) were judged as the "likely or possible" cause of death for 5 individuals.[57]

> Here, we describe the cardiac autopsy findings in five persons who have died unexpectedly within seven days following anti-SARS-CoV-2-vaccination, with vaccine-induced myocardial inflammation representing the likely or possible cause of death. Our findings establish the histological phenotype of lethal vaccination-associated myocarditis.

Schwab et al. *Clin Res Cardiol*. 2022 Nov 27:1–10.

* * *

Neuropathic and autonomic disorders should be added to *Section 6.2 Postmarketing Experience* of the label.

In May 2022, an NIH study reported on 23 patients reporting new neuropathic symptoms following vaccination.[58]

> **Conclusions:** This observational study suggests that a variety of neuropathic symptoms may manifest after SARS-CoV-2 vaccinations and in some patients might be an immune-mediated process.

Safavi et al. *medRxiv* [Preprint] (May 17, 2022)[58]

In December 2022, a study published in *Nature Cardiovascular Research* reported elevated risk of postural orthostatic tachycardia syndrome (POTS) and dysautonomia.[59]

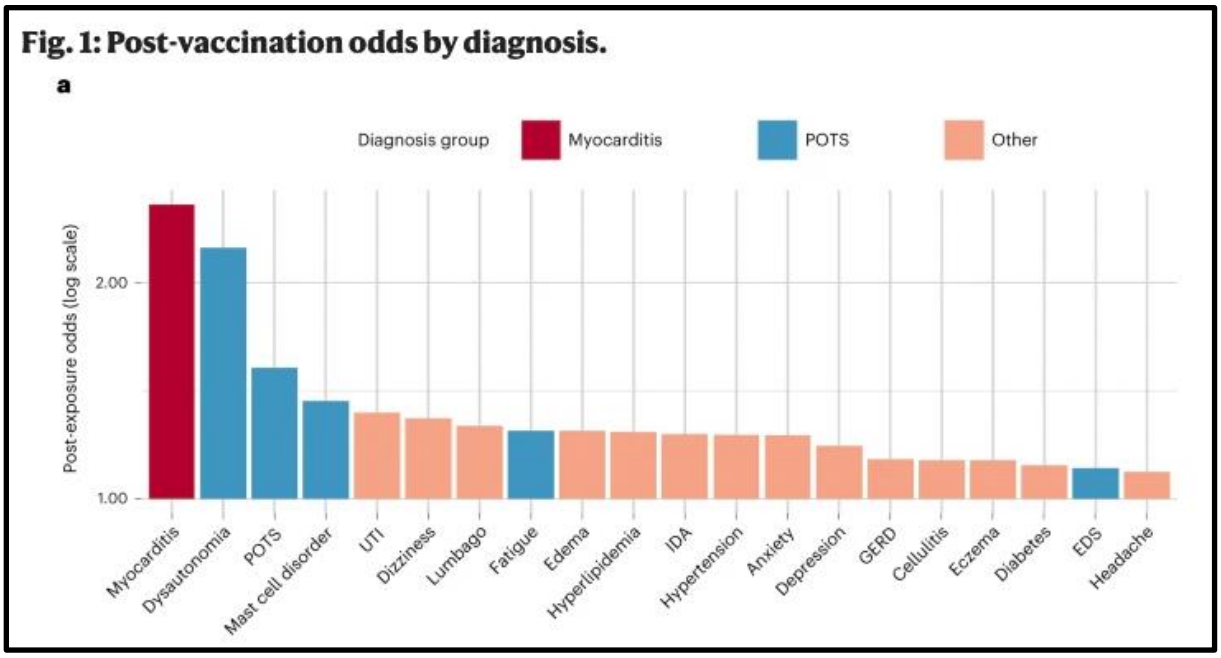


Figure 1 in Kwan et al. *Nat Cardiovasc Res 2022; 1:1187–1194.*

A linked editorial[60] discussing the study, stated that the research:

> *"undeniably establishes POTS and dysautonomia in general as adverse events after vaccination that should be recognized and investigated as other well-accepted post-vaccination syndromes, such as Guillain–Barre syndrome and acute disseminated encephalomyelitis."*[60]

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 [Pfizer only];
b. heavy menstrual bleeding;
c. detection of vaccine mRNA in breastmilk.

Decreased sperm concentration should be added to *Section 6.2 Postmarketing Experience* of the Pfizer label.

Section *13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility* of the Pfizer and Moderna labels states that neither vaccine has been studied for the potential to impair male fertility.[1,3]

> **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**
>
> COMIRNATY has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility. In a developmental toxicity study in rats with COMIRNATY there were no vaccine-related effects on female fertility *[see Use in Specific Populations (8.1)]*.

FDA-approved Pfizer vaccine label, p.21
(Similar language in Moderna vaccine label p.13)

A postmarketing study of sperm donors who had received Pfizer vaccine in Israel, published in *Andrology*, however, found that vaccination temporarily impairs semen concentration and total motile count among semen donors.[61]

The temporary decline in sperm concentration and total motile count should be added to product labeling.

> In conclusion, in this longitudinal multicenter study, we found a selective temporary decline of sperm concentration and total motile count 3 months post-vaccination followed by recovery among SD. While on first look, these results may seem concerning, from a clinical perspective they confirm previous reports regarding

Gat et al. *Andrology*. 2022 Sep;10(6):1016-1022.

* * *

Heavy menstrual bleeding should be added to *Section 6.2 Postmarketing Experience* of the label.

In October 2022, the European Medicines Agency (EMA) has advised that heavy menstrual be added to product labeling.

> **Comirnaty and Spikevax: heavy menstrual bleeding added as a side effect**
>
> The PRAC has recommended that heavy menstrual bleeding should be added to the product information as a side effect of unknown frequency of the mRNA COVID-19 vaccines Comirnaty and Spikevax.

European Medicines Agency website (Oct 28, 2022)[62]

An NIH-funded study published in *BMJ Medicine*, and reporting by the *New York Times* and *Washington Post*, have documented additional menstrual irregularities.[63–65]

At present, Pfizer and Moderna product labeling does not mention anything related to menstrual irregularities.

* * *

Detection of vaccine mRNA in breastmilk should be added to *Section 8.2 Lactation* of the label.

The Pfizer label states: "It is not known whether COMIRNATY is excreted in human milk."[1] (Identical language appears for Moderna's SPIKEVAX.[3])

However, a study published in *JAMA Pediatrics* has documented the presence of vaccine mRNA in breast milk for at least 48 hours after maternal vaccination.[66]

Table 2. Detection of Vaccine RNA in Whole Expressed Breast Milk and Extracellular Vesicles in 5 Patients at Various Time Points Postvaccination

Participant No.	Vaccine type	Time points of vaccine mRNA detection in EBM	Concentration of vaccine mRNA detected in whole milk[a]	Concentration of vaccine mRNA detected in EBM EVs[a]
4	BNT162b2	27-h[b] Sample	Not detected	14.01 pg/mL
6	mRNA-1273	27-h and 42-h[b] Samples	11.7 pg/mL	16.78 pg/mL
7	BNT162b2	37-h[b] Sample	Not detected	4.69 pg/mL
8	BNT162b2	1-h and 3-h[b] Samples	1.3 pg/mL	6.77 pg/mL
10	mRNA-1273	45-h[b] Sample	2.5 pg/mL	2.13 pg/mL

Abbreviation: EBM, expressed breast milk; EVs, extracellular vesicles; mRNA, messenger RNA.

[a] Units for concentration are picogram of mRNA per milliliter of whole milk equivalent.

[b] Sample used for vaccine mRNA concentration detection.

Table 2 in Hanna et al. *JAMA Pediatr*. 2022;176(12):1268–1270.

9. Add frequency data for clinical and subclinical myocarditis.

Current labeling provides no information on the frequency of myocarditis or pericarditis. 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).[67] For example, a prospective cohort study of 301 adolescents in Thailand measured cardiovascular outcomes following dose 2 of Pfizer vaccine. Myopericarditis was confirmed in one patient (1/301), two patients had suspected pericarditis, and 4 patients had suspected subclinical myocarditis.[68] A Hong-Kong cohort study of males 12-17 years old reported increased risk of myocarditis/pericarditis at 1/2700 following dose 2 of Pfizer vaccine.[69] And an FDA analysis estimated myocarditis/pericarditis increased risk at 1/5000 among vaccinated males 16-17 years old.[28]

In addition, the label states: "Information is not yet available about potential long-term sequelae."[1,3]

This statement is outdated, as studies now exist. For example, a CDC study in *The Lancet Child and Adolescent Health* found 50% (178/357) of adolescents with post-vaccine myocarditis had ≥1 symptom lasting at least 90 days from onset of myocarditis.[70]

> In the 2 weeks before the survey date, 178 (50%) of 357 patients reported having at least one symptom that might occur with myocarditis (chest pain or discomfort, fatigue, shortness of breath, or palpitations). Patients who were not considered recovered from myocarditis more frequently reported fatigue than did patients who were considered recovered (12 [43%] *vs* 40 [21%]; p=0·018; table 1). By contrast, based on the last patient encounter, health-care providers reported that 62 (16%) of 393 patients at least one symptom that might occur with myocarditis (table 1).

Kracalik et al. *Lancet Child Adolesc Health*. 2022 Nov;6(11):788-798.

10. Labeling should present trial results on serious adverse events in tables with statistics, as is done for non-serious adverse events.

The potential benefits of vaccination vary by population and over time. To enable providers to ensure benefits outweigh risks for individual patients, labeling should clearly convey the risk of serious adverse events.

Currently, product labeling and the EUA Fact Sheet report commonly experienced adverse events (redness, swelling, pain at injection site) in tabular format, as is expected.

However serious adverse events are **not** presented in tabular format. This prevents easy understanding of risk. FDA should require SAE be presented in tabular format e.g. similar to how Fraiman et al. presented the RCT data.[71]

Trial	Total events (events per 10,000 participants)[a] Vaccine	Placebo	Risk difference per 10,000 participants (95 % CI)[e]	Risk ratio (95 % CI)[e]
Serious adverse events				
Pfizer[b]	127 (67.5)	93 (49.5)	18.0 (1.2 to 34.9)	1.36 (1.02 to 1.83)
Moderna[c, d]	206 (135.7)	195 (128.6)	7.1 (–23.2 to 37.4)	1.06 (0.84 to 1.33)
Combined[f]	333 (98.0)	288 (84.8)	13.2 (-3.2 to 29.6)	1.16 (0.97 to 1.39)

Table 2 in Fraiman et al. Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. *Vaccine*. 2022 Sep 22;40(40):5798-5805.

III. ENVIRONMENT IMPACT

The petitioner hereby states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. Sections 25.30 and 25.31.

IV. ECONOMIC IMPACT

Economic impact information will be submitted upon request of the commissioner.

V. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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