



September 25th, 2020

Dr. Steven Hahn, Director FDA
Dr. Peter Marks, Director CBER

RE: [Phase III Moderna mRNA-1273 Vaccine](#)

Dear Drs. Hahn and Marks,

We are writing to you to request that the FDA and Center for Biological Evaluation and Research investigate Moderna's mRNA vaccine that contains polyethylene glycol (PEG), a molecule which approximately [8% of the U.S. population has highly elevated levels of antibodies](#). Injecting a PEG-containing vaccine into individuals with pre-existing PEG antibodies could lead to life-threatening [anaphylaxis](#).¹ Children's Health Defense has grave concerns that the [Phase III clinical trial of Moderna's mRNA-1273 SARS-CoV-2 vaccine](#) may be non-compliant with the Protection of Human Subjects, specifically:

1. 45 CFR 46.116(b) (2) that requires a description of any reasonably foreseeable risks or discomforts to the subject.
2. 45 CFR 46-111(a) (1) that requires that risks to clinical trial participants be minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk.

Moderna's mRNA vaccine, which has rapidly moved into [human clinical trials](#), relies on a new nanoparticle-based "carrier system" that utilizes polyethylene glycol (PEG). The lipid nanoparticles (LNPs) in the Moderna vaccine are coated with the synthetic, nondegradable and [increasingly controversial](#) PEG polymer in a process called PEGylation.

PEG is utilized in drug delivery and nanotechnology due to its reported "stealth" properties and alleged biocompatibility. In recent years, however, PEG has come under increasing [scrutiny](#).² Investigators who once assumed that the polymer was largely "inert" are now questioning its

¹ Wylon K, Dölle S, Worm M. Polyethylene glycol as a cause of anaphylaxis. *Allergy Asthma Clin Immunol.* 2016;12:67. <https://doi.org/10.1186/s13223-016-0172-7>

² Verhoef JJ, Anchordoquy TJ. Questioning the use of PEGylation for drug delivery. *Drug Deliv Transl Res.* 2013;3(6):499-503. [doi:10.1007/s13346-013-0176-5](https://doi.org/10.1007/s13346-013-0176-5)

[biocompatibility](#)³ and warning about PEGylated particles' promotion of tumor growth and adverse immune responses that include "probably underdiagnosed" life-threatening [anaphylaxis](#).⁴ These undesirable responses have, on occasion, halted clinical trials.⁵ As a result, some scientists argue that it is time to develop alternatives [to replace PEG](#). American and Dutch researchers [declared in 2013](#).⁶

[T]he accumulating evidence documenting the detrimental effects of PEG on drug delivery make it imperative that scientists in this field break their dependence on PEGylation.

Moderna documents and publications indicate that the company is well aware of safety risks associated with PEG and other aspects of its mRNA technology. In the corporate [prospectus](#) supporting Moderna's stock market launch in late 2018, the company was frank that its technical approach has numerous risks.

Specifically, Moderna acknowledged the potential for its proprietary lipid nanoparticles and PEG to produce "systemic side effects," given the scientific literature's documentation of these types of side effects for other LNPs. In comments not generally seen by the public, Moderna [stated](#) (p. 33):

[T]here can be no assurance that our LNPs will not have undesired effects. Our LNPs could contribute, in whole or in part, to one or more of the following: [immune reactions](#), [infusion reactions](#), [complement reactions](#), [opsonation reactions](#), [links added] [antibody reactions](#) . . . or reactions to the PEG from some lipids or PEG otherwise associated with the LNP. Certain aspects of our investigational medicines may induce immune reactions from either the mRNA or the lipid as well as adverse reactions within liver pathways or degradation of the mRNA or the LNP, any of which could lead to significant adverse events in one or more of our clinical trials.

Instead of expressing concern over clinical trial participants' welfare, that section of the prospectus concluded that any one of these problems "could materially harm [the company's] business, financial conditions, and prospects."

³ Betker JL, Anchordoquy TJ. The use of lactose as an alternative coating for nanoparticles. *J Pharm Sci.* 2020;109(4):1573-1580. doi:10.1016/j.xphs.2020.01.019

⁴ Wylon K, Dölle S, Worm M. Polyethylene glycol as a cause of anaphylaxis. *Allergy Asthma Clin Immunol.* 2016;12:67. <https://doi.org/10.1186/s13223-016-0172-7>

⁵ Ganson NJ, Povsic TJ, Sullenger BA, et al. Pre-existing anti-polyethylene glycol antibody linked to first-exposure allergic reactions to pegnivacogin, a PEGylated RNA aptamer. *J Allergy Clin Immunol.* 2016;137(5):1610-1613.e7. <https://doi.org/10.1016/j.jaci.2015.10.034>

⁶ Verhoef JJ, Anchordoquy TJ. Questioning the use of PEGylation for drug delivery. *Drug Deliv Transl Res.* 2013;3(6):499-503. doi:10.1007/s13346-013-0176-5

Such concerns stem from that fact that PEG-specific immune responses can actually *reduce* the efficacy of vaccines and *increase* the occurrence of adverse events. A [2016 study](#)⁷ in *Analytical Chemistry* reported detectable and sometimes high levels of anti-PEG antibodies (including first-line-of-defense IgM antibodies and later stage IgG antibodies) in approximately [72% of contemporary human samples](#) and about 56% of historical specimens from the 1970s through the 1990s. Of the 72% with PEG IgG antibodies, 8% had anti-PEG IgG antibodies greater than 500ng/ml., which is considered extremely elevated. Extrapolated to the U.S. population of 330 million who may receive this vaccine, 16.6 million may have antibody levels associated with adverse effects. The researchers confessed that the results were entirely unexpected. The authors concluded that ***“...sensitive detection and precise quantitation of anti-PEG Ab levels in a clinical setting will be essential to ensuring the safe use of PEGylated drugs in all target patient populations going forward.”***

On July 28th, a member of Children’s Health Defense who suffers with anaphylactic PEG reactions wrote to CovPN citing the 2016 study’s conclusions and asking the following question: “As Moderna’s mRNA-1273 candidate vaccine uses a PEGylated LNP vector, what procedures are included in the trial to mitigate this risk?” The response from CovPN is quoted below.

“Thank you so much for this scientific question. I consulted with several of the physician scientists working on the Moderna study, and they have provided me with this response to send on to you:

*Pre-existing antibody levels, along with various genetic polymorphisms, may impact the safety profile of a biomedical intervention in a variety of populations. If there are significant safety signals from the CoVPN clinical trials, all efforts will be made to understand the mechanisms that may have contributed to these signals. **Pre-screening populations based on hypothesized biomarkers, such as anti-PEG antibodies, is not a strategy currently employed in our clinical trials.**”*

While the Moderna scientists allege that PEG antibody development is purely hypothetical, the scientific literature clearly documents that the immune system can and does form antibodies against PEG (anti-PEG Abs) in both animals and humans.^{8 9 10 11} The existence of anti-PEG

⁷ Yang Q, Jacobs TM, McCallen JD, et al. Analysis of pre-existing IgG and IgM antibodies against polyethylene glycol (PEG) in the general population. *Anal Chem.* 2016;88(23):11804-11812. doi:10.1021/acs.analchem.6b03437

⁸ Garay RP, El-Gewely R, Armstrong JK, Garratty G, Richette P. Antibodies against polyethylene glycol in healthy subjects and in patients treated with PEG-conjugated agents. *Expert Opin Drug Deliv.* 2012;9:1319-1323. doi: 10.1517/17425247.2012.720969

⁹ Zhang P, Sun F, Liu S, Jiang SJ. Anti-PEG antibodies in the clinic: current issues and beyond PEGylation. *J Control Release.* 2016;244:184-193. doi: 10.1016/j.jconrel.2016.06.040

¹⁰ Yang Q, Lai SK. Anti-PEG immunity: emergence, characteristics, and unaddressed questions. *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* 2015;7:655-677. doi: 10.1002/wnan.1339

¹¹ Sherman MR, Williams LD, Sobczyk MA, Michaels SJ, Saifer MG. Role of the methoxy group in immune responses to mPEG protein conjugates. *Bioconjug Chem.* 2012;23:485-499. doi: 10.1021/bc200551b

antibodies threatens patient safety through possible anaphylaxis reactions^{12 13 14} and re-exposure to PEG-containing drugs may greatly increase the chance for adverse effects due to B cell memory of anti-PEG Abs.¹⁵

The 2016 *Analytical Chemistry* findings and other studies indicate the widespread occurrence of anti-PEG Abs in the general population due to daily exposure to PEG-containing products.^{16 17} The population's increased exposure to PEG-containing products makes it “natural to assume” that anti-PEG antibodies will continue to be widespread.” If high-titer anti-PEG Abs are present in blood, even people without known allergies may have severe hypersensitivity reactions when receiving PEG-containing therapeutics for the first time.^{18 19}

Thus, screening for and monitoring the levels of anti-PEG antibodies in blood before and during treatment with PEG-containing drugs are of particular importance to improve safety and maintain therapeutic efficacy.²⁰

According to ClinicalTrials.gov, Moderna started enrollment for the Phase 3 study of its mRNA vaccine on July 28, 2020 and plans to enroll 30,000 participants in the study over the next two years. For those participating in the Moderna clinical trials, the uptick in parenteral exposure to PEG will be unprecedented—potentially disastrous and life-threatening.

¹² Hershfield MS, Ganson NJ, Kelly SJ, Scarlett EL, Jagers DA, Sundy JS. Induced and pre-existing anti-polyethylene glycol antibody in a trial of every 3-week dosing of pegloticase for refractory gout, including in organ transplant recipients. *Arthritis Res Ther*. 2014;16:R63. doi: 10.1186/ar4500

¹³ Ganson NJ, Povsic TJ, Sullenger BA, et al. Pre-existing anti-polyethylene glycol antibody linked to first-exposure allergic reactions to pegnivacogin, a PEGylated RNA aptamer. *J Allergy Clin Immunol*. 2016;137:1610-1613. doi: 10.1016/j.jaci.2015.10.034

¹⁴ Povsic TJ, Lawrence MG, Lincoff AM, et al. Pre-existing anti-PEG antibodies are associated with severe immediate allergic reactions to pegnivacogin, a PEGylated aptamer. *J Allergy Clin Immunol*. 2016;138:1712-1715. doi: 10.1016/j.jaci.2016.04.058

¹⁵ Longo N, Harding CO, Burton BK, et al. Single-dose, subcutaneous recombinant phenylalanine ammonia lyase conjugated with polyethylene glycol in adult patients with phenylketonuria: an open-label, multicentre, phase I dose-escalation trial. *Lancet*. 2014;384:37-44. doi: 10.1016/S0140-6736(13)61841-3

¹⁶ Yang Q, Jacobs TM, McCallen JD, et al. Analysis of pre-existing IgG and IgM antibodies against polyethylene glycol (PEG) in the general population. *Anal Chem*. 2016;88:11804-11812. doi: 10.1021/acs.analchem.6b03437

¹⁷ Chen BM, Su YC, Chang CJ, et al. Measurement of pre-existing IgG and IgM antibodies against polyethylene glycol in healthy individuals. *Anal Chem*. 2016;88:10661-10666. doi: 10.1021/acs.analchem.6b03109

¹⁸ Ganson NJ, Povsic TJ, Sullenger BA, et al. Pre-existing anti-polyethylene glycol antibody linked to first-exposure allergic reactions to pegnivacogin, a PEGylated RNA aptamer. *J Allergy Clin Immunol*. 2016;137:1610-1613. doi: 10.1016/j.jaci.2015.10.034

¹⁹ Povsic TJ, Lawrence MG, Lincoff AM, et al. Pre-existing anti-PEG antibodies are associated with severe immediate allergic reactions to pegnavacogin, a PEGylated aptamer. *J Allergy Clin Immunol*. 2016;138:1712-1715. doi: 10.1016/j.jaci.2016.04.058

²⁰ Zhang P, Sun F, Hung H-C, Jain P, Leger KJ, Jiang S. Sensitive and quantitative detection of anti-poly(ethylene glycol) (PEG) antibodies by methoxy-PEG-coated surface plasmon resonance sensors. *Anal Chem*. 2017;89:8217-8222. doi: 10.1021/acs.analchem.7b02447

As the excerpts from the Moderna prospectus illustrate, Moderna scientists are [fully aware](#) of PEG-related safety concerns. In the prospectus, Moderna admits that “unacceptable health risks or adverse side effects” could make it difficult to recruit or retain clinical trial participants and also that an “unfavorable benefit risk ratio could [inhibit market acceptance](#)” if their product proceeds to market. Addressing the efficacy side of the equation, a mid-2019 study by authors who “are or have been employees of Moderna, Inc. and receive salary and stock options from Moderna, Inc.” further admitted that anti-PEG antibodies “present [significant challenges](#) to the clinical efficacy of PEGylated therapeutics and will require strategies to overcome [their] effects.”

Moderna reported results from the Phase 1 open-label trial in 45 healthy adults in the *New England Journal of Medicine* on July 14th, 2020.²¹ Over half (23 out of 45) of the participants experienced a vaccine adverse event.

*After the first vaccination, solicited systemic adverse events were reported by 5 participants (33%) in the 25- μ g group, 10 (67%) in the 100- μ g group, and 8 (53%) in the 250- μ g group; all were mild or moderate in severity (Figure 1). Solicited systemic adverse events were more common after the second vaccination and occurred in 7 of 13 participants (54%) in the 25- μ g group, all 15 in the 100- μ g group, and all 14 in the 250- μ g group, with **3 of those participants (21%) reporting one or more severe events.***

What is most concerning is that one of the participants in the lowest exposure group, 25- μ g, developed urticaria (hives) five days after the first vaccination and ultimately withdrew from the study. Urticaria is an allergic response often associated with drug reactions which may be mild and self-limiting or present as a [severe allergic reaction \(anaphylaxis\)](#) that is life-threatening-requiring immediate emergency treatment.

Children’s Health Defense has grave safety and efficacy concerns about the use of PEG in vaccines due to the high percentage of the population having pre-existing antibodies to PEG. While it unlikely that everyone with pre-existing PEG antibodies will have a severe reaction to a vaccine containing PEG, it is dangerous to assume that none will. Because Moderna’s trial is not pre-screening participants for anti-PEG antibodies, the trial investigators will not be able to assess the risk.

Multiple previous studies regarding the prevalence of anti-PEG antibodies in the population have stated that pre-screening should be done prior to any administration of a PEG-containing medication. Screening is likely to be even more important in the case of a vaccine intended for parenteral administration to as many people as possible that contains a substance to which the majority of the population unknowingly has antibodies. Not characterizing trial participants’ adverse reactions in relation to anti-PEG antibody presence and levels eliminates insights into these interactions and is a missed opportunity to prevent harmful adverse events.

²¹ Jackson LA, Anderson EJ, Roupheal NG, et al. An mRNA vaccine against SARS-CoV-2—preliminary report. *N Engl J Med*. 2020 Jul 14;NEJMoa2022483. doi: 10.1056/NEJMoa2022483

Dismissing the proven fact that a high percentage of the population has anti-PEG antibodies as merely “hypothetical,” Moderna’s statement that it will not screen for them is dangerous to the trial participants and in violation of 45 CFR 46.116(b)(2) that requires a description of any reasonably foreseeable risks or discomforts to the subjects and 45 CFR 46-111(a) (1) that requires that risks to clinical trial participants be minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk.

Children’s Health Defense strongly recommends that the following steps be taken immediately to assure true informed consent and to prevent an unnecessary risk to the clinical trial participants:

- That ALL trial participants be notified that the Moderna vaccine contains PEG.
- That the study questionnaire screen all applicants for a history of PEG allergy.

Additional steps must be taken to reduce the risk of exposing trial participants to a substance to which up to 72% of the U.S. population has pre-existing antibodies.

These steps should include:

- Pre-screening trial participants for the presence and titers of anti-PEG antibodies.
- Using such data to characterize the potential association and impact of anti-PEG antibodies on adverse reactions in the trial.
- Identifying the level of anti-PEG antibody titers that precludes safe administration of the vaccine in the absence of secondary measures to address the anti-PEG immune response.
- Measuring the impact of the anti-PEG immune response on vaccine efficacy.

We would appreciate a timely review of our critical concerns as enrollment is underway and time is of the essence in protecting those individuals with PEG antibodies from unnecessary exposure and harm. Please contact Ms. Redwood if you have any questions regarding the complaint. She can be reached at 404-932-1786.

Warmest regards,

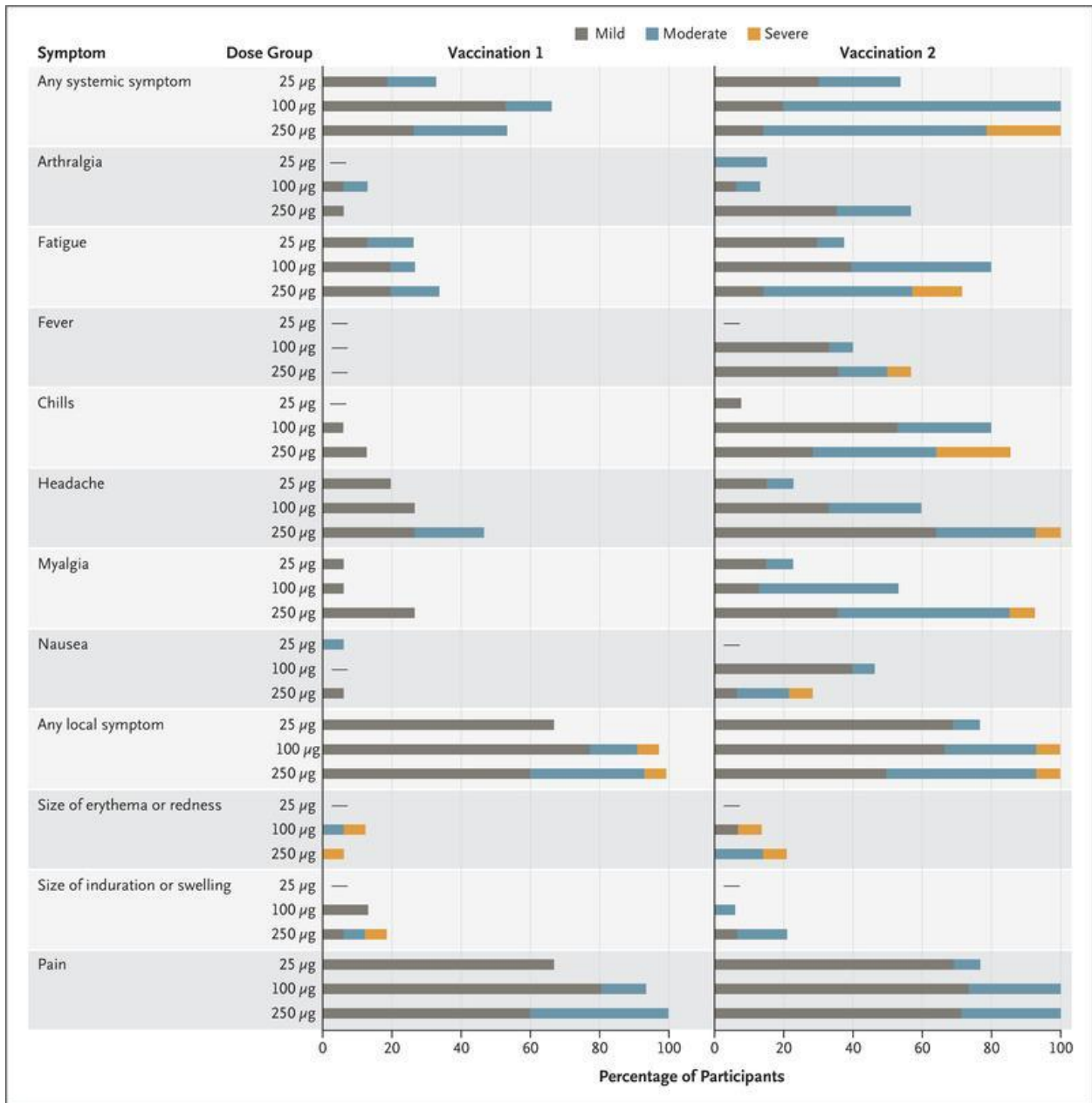
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cc. Lisa Buchanan, Congressman Bill Posey, Senator Tim Kaine, Laurie Doepel, Dr. Anthony Fauci, Hugh Auchincloss, John Mascola, Cliff Lane

(Figure 1)



References