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**VIA EMAIL AND FEDEX**

January 19, 2023

Robert M. Califf, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
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commissioner@fda.hhs.gov

Keith Peden, PhD
Office of Vaccines Research and Review
Division of Viral Products
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Re: *Corrections Sought Regarding Presentation at FDA NanoDay Symposium, October 11, 2022 and Request for Needed Safety Testing on Novel Lipid Nanoparticle*

Dear Commissioner Califf and Dr. Peden:

We write on behalf of our client, Informed Consent Action Network ("**ICAN**"), regarding the presentation of Keith Peden, Chief of the Laboratory of DNA Viruses, during the FDA's October 11, 2022, NanoDay Symposium, titled, "Considerations for the Quality, Safety and Efficacy of Prophylactic Lipid Nanoparticle mRNA Vaccines." ICAN requests that the FDA immediately (i) take additional steps to assess the safety of the novel lipid nanoparticle excipient, as used in COVID-19 vaccines, and (ii) issue a correction regarding the above-referenced presentation and ensure that it comports with the most recent evidence from the biomedical literature.

## I. The Lipid Nanoparticle in mRNA Vaccines Should Have Been Separately Assessed for Safety Pursuant to Industry Guidelines

Both the Pfizer and Modern COVID-19 mRNA vaccines are formulated in lipid nanoparticles, designed to facilitate delivery of the mRNA into host cells.[1] During the Symposium, Dr. Peden stated that a decision was made to classify the lipid nanoparticle component of the mRNA vaccines as an "excipient" rather than an active pharmaceutical ingredient. Dr. Peden further explained that the mRNA in the vaccine vial was characterized as the "drug substance" and "equivalent of the active ingredient."[2]

[1] Pfizer Package Insert, https://www.fda.gov/media/151707/download; Moderna Package Insert, https://www fda. gov/media/144637/download.

[2] Dr. Peden briefly mentioned that the lipid nanoparticles were evaluated by Absorption-Distribution-Metabolism-Excretion-Toxicity; however, he did not cite any data on this point during the presentation nor did he describe any of the other safety assessment protocols recommended by FDA guidance for novel excipients.

Given that the lipid nanoparticles employed in both the Pfizer and Moderna mRNA platforms were defined as "excipients" and are novel excipients,[3] they should have been analyzed and separately assessed for safety. This is what the FDA's guidelines call for, as set forth in its "Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients" concerning the development of safety profiles to support use of novel excipients as components of drug or biological products.[4]

As such, the FDA should have followed its own industry guidelines and required Pfizer and Moderna to separately assess the safety of these novel excipients *prior to their use* in mRNA vaccines. This includes fully qualifying their safety with regard to proposed level of exposure, duration of exposure, or route of administration.

In sum, given that the FDA defined the lipid nanoparticles in the mRNA COVID-19 vaccines as excipients, and given that "adequate prior human exposure has not been documented,"[5] the following industry guidelines are applicable pursuant to FDA's own published guidance (the vast majority of which have not been complied with by Pfizer or Moderna):

a) **Safety Pharmacology.** Pivotal toxicology studies should be performed, and novel excipients evaluated for pharmacological activity using a battery of standard tests based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("**ICH**") guidance S7A (safety pharmacology studies for human pharmaceuticals).[6]

b) **Safety Evaluation for Potential Excipients Intended for Short-Term Use.** Since mRNA vaccines are limited by their labeling to clinical use of 14 or fewer consecutive days per treatment, they fall within the short-term use guidance. Recommendations for their evaluation are, at minimum, the following:

- Acute toxicology studies[7]
- Absorption, distribution, metabolism, and excretion analyses of the excipient following administration by the clinically relevant routes[8]
- Genetic toxicology tests[9]

[3] Bruce Yihua Yu, *et al.*, *Excipient Innovation Through Precompetitive Research*, Pharm. Res. (Dec. 20, 2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8687151/.

[4] *Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, FDA (May 2005), https://www.fda.gov/media/72260/download.

[5] *Id.* at 4.

[6] *Id.*

[7] *Id.* at 5.

[8] *Id.*

[9] *Id.*

- One month repeat-dose toxicology studies in a rodent and mammalian nonrodent species[10]
- Reproductive toxicology evaluation pursuant to ICH guidelines S5A and S5B[11]

**c) Safety Evaluation of Excipients for Use in Injectable Products.** Since both mRNA vaccines are indicated for administration by way of injection, this section of the guidance is applicable and the following are recommended:

- Perform "[a]ll studies from Section IV.A., B., C., or D., as appropriate, using the appropriate route of administration. Studies that include the to-be-marketed formulation of the drug product are preferred, if this information is available at the time of excipient evaluation."[12]
- Conduct a sensitization study.[13]
- Investigate the hemolytic potential of the excipient.
- Assess plasma concentrations of creatinine kinase (correlate of potential muscle damage).
- Evaluate protein binding in connection with local site tolerability.
- Obtain photo-safety data (evaluation of adverse event potential in the presence of light) on the excipient or complete drug product.[14]

Despite the FDA's own guidelines for novel excipients, it appears that little if any of the foregoing minimal risk assessment testing has been conducted on the novel lipid nanoparticle excipient. If such testing has been performed, please provides copies of same to the public forthwith.

## II. Modification of Nucleosides Within the mRNA in C-19 Vaccines Poses Known Risks

In response to a question posed at the NanoDay Symposium concerning nucleoside modification within the mRNA in COVID-19 vaccines, Dr. Peden stated that such modification poses little hazard becasue the nucleosides are substituted with "naturally occurring nucleosides." However, this assertion is doubtful at best and false at worst given the existing biomedical literature reflecting potentially harmful consequences that can result from nucleoside modification.

Specifically, Dr. Peden noted that $N^1$-methylpseudouridine supplants uridine in the nucleotide sequence. The artificial substitution of this genetic sequence with $N^1$-methylpseudouridine has been shown to interfere with the immune system by suppressing the activity of key cells and immune molecules involved in the front-line defenses of the human

[10] *Id.*

[11] *Id.* at 5-6.

[12] *Id.* at 8.

[13] *Id.*

[14] *Id.*

body.[15] This was a significant finding, as this may have potential impacts on COVID-19 vaccine recipients by reducing their capacity to produce an innate immune response.

A 2022 paper by researchers at the University of Pennsylvania School of Medicine further explained this risk by assessing the impact of nucleoside modification. In it, the researchers, referencing the in vitro experiments performed in the above-mentioned 2005 study, concluded that this nucleotide sequence modification (uridine to pseudouridine) could cause a profound innate immunity suppression.[16] The paper also discussed a study conducted by Belgian researchers in conjunction with the Massachusetts Institute of Technology which discovered that the nucleoside used in the mRNA vaccines (methylpseudouridine) is very effective at suppressing the body's front-line defenses (innate immune system).[17] These findings are highly concerning considering that both mRNA vaccines employ this nucleoside modification,[18] and such modification can suppress the innate immune system, a major key in preventing and fighting infection,[19] as well as cancers,[20] among other important functions. Significantly, vaccine developers have acknowledged that "[v]accine RNA can be modified by incorporating 1-methylpseudouridine, which dampens innate immune sensing and increases mRNA translation in vivo."[21]

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[15] Katalin Karikó, *et al.*, *Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA*, Immunity (Aug. 23, 2005), https://www.sciencedirect.com/science/article/pii/S1074761305002116 (This seminal 2005 study elucidated that nucleoside modifications such as substitution of uridine with pseudouridine - one of the most abundant modifications - "along with the other uridine modifications m5U and s2U uniquely suppress the capacity of RNA to activate primary dendritic cells." It is well established that dendritic cells play an integral role in many immunomodulatory functions, including assisting in the induction of an adaptive and innate immune response. The study demonstrated that "RNA signals through human TLR3, TLR7, and TLR8, but incorporation of modified nucleosides m5C, m6A, m5U, s2U, or pseudouridine ablates activity").

[16] Stephanie Seneff, *et al.*, *Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and MicroRNAs*, Food & Chemical Toxicology (Apr. 15, 2022), https://www.sciencedirect.com/science/article/pii/S027869152200206X (noting that "a simple modification to the mRNA such that all uridines were replaced with pseudouridine could dramatically reduce innate immune activation against exogenous mRNA").

[17] *Id.*; Oliwia Andries, *et al.*, *N1-methylpseudouridine-incorporated mRNA outperforms pseudouridine-incorporated mRNA by providing enhanced protein expression and reduced immunogenicity in mammalian cell lines and mice*, Journal of Controlled Release (Sept. 3, 2015), https://www.sciencedirect.com/science/article/abs/pii/S0168365915300948 (finding "that 1-methylpseudouridine as a replacement for uridine was even more effective than pseudouridine and could essentially abolish the TLR response to the mRNA, preventing the activation of blood-derived dendritic cells").

[18] Jung Woo Park, *et al.*, *mRNA vaccines for COVID-19: what, why and how*, International Journal of Biological Sciences (Apr. 10, 2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8071766/.

[19] Jean Marshall, *et al.*, *An introduction to immunology and immunopathology*, Allergy, Asthma & Clinical Immunology (Sept. 12, 2018), https://aacijournal.biomedcentral.com/articles/10.1186/s13223-018-0278-1 (noting "[a]n important function of innate immunity is the rapid recruitment of immune cells to sites of infection and inflammation through the production of cytokines and chemokines").

[20] Srikrishnan Rameshbabu, *et al.*, *Targeting Innate Immunity in Cancer Therapy*, Vaccines (Basel) (Feb. 9, 2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7916062/. ("The role of the innate immune system in tumor immunosurveillance and generation of antitumor immune responses has been long recognized.").

[21] *See supra* note 18; Mark Mulligan, *et al.*, *Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults*, Nature (Aug. 12, 2020), https://pubmed ncbi.nlm.nih.gov/32785213/; Katalin Karikó, *et al.*, *Incorporation of pseudouridine*

## III. Other Harms Associated with Lipid Nanoparticles Ignored by FDA and CDC

In addition to the potential impacts already discussed, lipid nanoparticles can engender coagulation/clotting by way of their positively charged surface.[22] A study on a rat and monkey found that, after an intravenous infusion of mRNA lipid nanoparticles, coagulation parameters changed, necrotic (dying) tissue was observed, as well as other effects such as liver injury.[23] Lipid nanoparticles provoke strong inflammatory responses, activating a number of inflammation markers in the immune system, as evidenced by studies on mice.[24] Such responses, and activation of other immune pathways, can bring about a systemic toxicity, as shown by this Israeli study on mice.[25] It is also highly concerning that the CDC has been aware of such potential lipid nanoparticle-induced toxicity for nearly a decade.[26]

## IV. Vaccine Efficacy Values Should be Updated to Reflect Recent Empirical Data

Dr. Peden presented vaccine efficacy data in his presentation, citing two disparate studies which found efficacy values of 95% and 94% for the Pfizer and Moderna vaccines, respectively. Dr. Peden knew, or certainly should have known, that this claimed efficacy was no longer valid. As one example, a synthesis of studies conducted by vaccine enthusiasts have found the vaccine at best provides only 40-50% efficacy against omicron infection.[27] See the below figure, which clearly depicts the rapidly declining efficacy values for the Omicron variant. The published presentation should be updated immediately to note that the claimed efficacy figures were outdated.

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*into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability*, Molecular Therapy (Sep. 16, 2008), https://pubmed.ncbi.nlm.nih.gov/18797453/.

[22] Claudia Sperling, *et al.*, *A Positively Charged Surface Triggers Coagulation Activation Through Factor VII Activating Protease (FSAP)*, ACS Appl. Mater. Interfaces (Nov. 1, 2017), https://www.duo.uio.no/bitstream/handle/10852/61833/Sperling%2Bet%2Bal.pdf?sequence=1&isAllowed=y.

[23] Maja Sedic, *et al.*, *Safety Evaluation of Lipid Nanoparticle–Formulated Modified mRNA in the Sprague-Dawley Rat and Cynomolgus Monkey*, Veterinary Pathology (Nov. 30, 2017), https://journals.sagepub.com/doi/10.1177/0300985817738095?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed.

[24] Sonia Ndeupen, *et al.*, *The mRNA-LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory*, iScience (Dec. 17, 2021), https://pubmed ncbi.nlm nih.gov/34841223/.

[25] Ranit Kedmi, *et al.*, *The systemic toxicity of positively charged lipid nanoparticles and the role of Toll-like receptor 4 in immune activation*, Biomaterials. (June 11, 2010), https://pubmed ncbi.nlm nih.gov/20541799/.

[26] Amruta Manke, et al., Mechanisms of Nanoparticle-Induced Oxidative Stress and Toxicity, Biomed Res. Int. (July. 16, 2013), https://stacks.cdc.gov/view/cdc/21130.

[27] *COVID-19 vaccine efficacy summary*, IMHE (Nov. 18, 2022), https://www.healthdata.org/covid/covid-19-vaccine-efficacy-summary.

| | Effectiveness at preventing | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ancestral | | Alpha | | Beta | | Gamma | | Delta | | Omicron | |
| Vaccine | Severe disease | Infection | Severe disease | Infection | Severe disease | Infection | Severe disease | Infection | Severe disease | Infection | Severe disease | Infection |
| Johnson & Johnson | 86% | 72% | 86% | 72% | 76% | 64% | 76% | 64% | 76% | 64% | 57% | 33% |
| Moderna | 97% | 92% | 97% | 92% | 97% | 91% | 97% | 91% | 97% | 91% | 73% | 48% |
| Novavax | 89% | 83% | 89% | 83% | 86% | 82% | 86% | 82% | 86% | 82% | 65% | 43% |
| Pfizer/BioNTech | 95% | 86% | 95% | 86% | 95% | 84% | 95% | 84% | 95% | 84% | 72% | 44% |

## V. Actions Requested

In light of the above, ICAN requests the following:

1. Provide the safety assessments outlined in Section I for the mRNA vaccine excipient – the lipid nanoparticles – in the Moderna and Pfizer mRNA vaccines, or explain why one or more of these assessments were not performed.

2. Issue an update and correction to the assertions regarding the purported absence of risk posed via modification of nucleosides.

3. Issue an update and correction to the data presented concerning vaccine efficacy.

We look forward to your prompt response.

Very truly yours,

Aaron Siri, Esq.
Elizabeth A. Brehm, Esq.
Thomas Stavola, Esq.