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VIA ELECTRONIC FILING

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Department of Health and Human Services
Food and Drug Administration
Commissioner Stephen M. Hahn, M.D.
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UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES AND THE FOOD AND DRUG ADMINISTRATION

PETITION FOR ADMINISTRATIVE ACTION REGARDING PHASE III CLINICAL TRIAL OF mRNA-1273 - NCT04470427	**:**	**Docket No.**

CITIZEN PETITION

This petition for administrative action is submitted on behalf of Informed Consent Action Network[1] ("**Petitioner**") pursuant to 21 CFR § 10.35 and related and relevant provisions of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act to request the Commissioner of Food and Drugs (the "**Commissioner**") require that the Phase III trial of mRNA-1273 (NCT04470427) conforms with the requests in the "Action Requested" section below before licensure.

Because of 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 Commissioner deny its Petition, **Petitioner respectfully requests that FDA act on the instant Petition and related petition for stay of action by August 26, 2020.**

[1] Including, but not limited to, on behalf of its members that work for the Petitioner.

A. ACTION REQUESTED

1. It is hereby requested that the study design for the Phase III trial of mRNA-1273 (NCT04470427)[2] be amended to provide that:

a. any and all adverse events and reactions[3] will be documented for the entire duration of the trial;

b. such documenting of adverse events and reactions shall last at least twelve months for adults, thirty-six months for children, and sixty months for infants and toddlers;

c. it uses an adequate sample size, appropriately powered, in order to (i) detect an increase in rare adverse events or, any untoward medical occurrence, whether or not considered vaccine related, and (ii) determine that the rate of adverse events from the vaccine will not exceed the rate of adverse events known to occur from SARS-CoV-2 in the group under review;[4] and

d. participants are tested for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination.

B. STATEMENT OF GROUNDS[5]

2. The current study design for the Phase III clinical trial for mRNA-1273 provides that, despite reviewing efficacy for at least 2 years, it will only capture "systemic adverse events" for 7 days after each dose and "unsolicited adverse events" for only 28 days after each dose. Beyond these extremely short safety review periods, an adverse event will only be captured if it results in the study participant withdrawing from the study, which is nonsensical since after getting two doses at the start of the study, there is little for a participant to withdraw from thereafter.[6] Limiting the review of safety in this manner is unethical and concerning given that the trial could easily and simply capture all adverse events for its entire duration.

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[2] NCT04470427 available at https://www.clinicaltrials.gov/ct2/show/NCT04470427 (last visited August 11, 2020).

[3] Including, but not limited to, systemic adverse reactions, adverse events, non-serious adverse event, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue of any degree or type arising or exacerbated post-vaccination, whether suspected, unexpected, expected or otherwise, and whether or not considered related to the vaccine.

[4] For example, for children, the clinical trial should be properly sized and powered to determine that the vaccine is safer than a child having a SARS-CoV-2 infection.

[5] The Petitioner hereby incorporates by reference as if fully set forth herein the Statement of Grounds from its Amended Citizen's Petition, dated July 20, 2020, available at, https://beta.regulations.gov/document/FDA-2020-P-1601-0028 (last visited August 11, 2020).

[6] *See* https://www.clinicaltrials.gov/ct2/show/NCT04470427 (last visited August 11, 2020).

3. The current study design is also underpowered as it will not be able to validate that the adverse event rate from this product is less than the adverse events caused by SARS-CoV-2 in each age group in which it seeks licensure. It also fails to test for T-cell reactivity pre-and-post vaccination which will call any resulting efficacy conclusion into question.

4. Petitioner will suffer irreparable harm if the action requested herein is not granted because once the FDA licenses this COVID-19 vaccine, states are expected to make this product mandatory. For example, the New York State Bar Association recently issued a report on COVID-19 recommending that "[w]hen the efficacy of a COVID-19 vaccine has been confirmed, enact legislation requiring vaccination of each person unless the person's physician deems vaccination for his or her patient to be clinically inappropriate."[7] Hence, without the FDA assuring proper safety trials of the vaccine *now*, the Petitioner will not have the opportunity to object to receiving the vaccine based on deficient clinical trials *later*.

5. Furthermore, as noted, ethical considerations prevent a placebo-controlled study post-licensure; thus, if the vaccine is licensed without an appropriate safety review, there will be no opportunity for any such study to ever occur. This is especially troubling because when parents assert that a licensed vaccine injured their child, the CDC regularly denies these assertions by stating that no cause and effect has been established between vaccination and the alleged injury. But as the FDA and CDC are well aware, *without* a placebo control trial, cause and effect is very difficult and often impossible to establish.[8] Therefore, no matter how many or what type of vaccine injuries are reported post licensure, the FDA, CDC, and manufacturers retort is that "a cause and effect relationship with the vaccine has not been established."[9] The FDA can avoid this ethical and conflict ridden quagmire now by issuing the stay and requiring the basic amendments to the trial design requested in this petition.

6. The public interest also weighs strongly in favor of the requested relief because having adequate safety review protocols will comport with the best interests of all Americans slated to receive this product and will increase public confidence in the safety and efficacy of this product.

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[7] https://nysba.org/app/uploads/2020/05/HealthLawSectionTaskForceCOVID-19Report_5.13.20-1.pdf (last visited August 11, 2020).

[8] *See* https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/adverse-reactions.html ("establishing evidence for cause and effect on the basis of case reports and case series alone is usually not possible," rather, researchers need "to compare the incidence of the event among vaccinees with the incidence among unvaccinated persons") (last visited August 11, 2020); *see also* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3505292/ (The entire advantage of a randomized placebo-controlled trial "is the ability to demonstrate causality i.e., cause-effect relationship.") (last visited August 11, 2020); https://www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html (The Vaccine Adverse Events Reporting System (VAERS) is unable "to determine causation" because "there is a lack of an unvaccinated group for comparison in VAERS.") (last visited August 11, 2020).

[9] *Id*.

a. Tracking All Adverse Events

7. To increase assurance that potential adverse events from mRNA-1273 are captured, all adverse events and reactions should be documented for each subject post-vaccination – whether or not they are considered vaccine-related by the investigator or sponsor – for the entire duration of the clinical trial.[10] All adverse events and reactions includes, but is not limited to, all systemic adverse reactions, adverse events, non-serious adverse events, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue of any degree or type arising or exacerbated post-vaccination, whether suspected, unexpected, expected or otherwise, and whether or not considered related to the vaccine.

8. As noted above, the current study design for the Phase III clinical trial for mRNA-1273 provides that, despite reviewing efficacy for at least 2 years, the current trial design for this vaccine will only capture "systemic adverse events" for 7 days after each dose and "unsolicited adverse events" for only 28 days after each dose.[11] Incredibly, beyond these extremely short safety review periods, adverse events will only be captured if it results in the study participant withdrawing from the study.[12] This is nonsensical since after getting two doses during the first 28 days of the clinical trial, there is little for a participant to withdraw from thereafter.[13] Once they have received both doses, if anything, a participant would have an incentive to remain part of the follow-up to address any adverse effects.

9. Moreover, there are many autoimmune, neurological, and chronic health disorders which have a major impact on the quality of life that this vaccine could cause which would be ignored simply because the participant did not withdraw from the study. For example, there are a myriad of post-licensure adverse reactions reported by consumers and physicians and also listed in the package inserts for one or more vaccines, including, for example: alopecia, autoimmune disease, lupus erythematosus, vasculitis, Bell's Palsy, hypotonia, migraine, myelitis, neuropathy, seizures, mental disorders, rhinitis, and vertigo.[14] But yet as long as the participant does not withdraw these will nonsensically be ignored as if they did not occur. This is unethical and renders any claim of safety for this product based on this trial vacuous.

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[10] *See* https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32 (last visited August 11, 2020) (defining "Adverse event" as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related"); *see also* https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event (last visited August 11, 2020).

[11] https://www.clinicaltrials.gov/ct2/show/NCT04470427 (last visited August 11, 2020).

[12] *Id.*

[13] *Id.*

[14] *See* https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm (last visited August 11, 2020). Also, the determination of whether an adverse reaction is a "serious adverse event" is typically left to the discretion of the sponsor of the clinical trial or the clinical investigators, who are paid by the sponsor, and therefore subject to bias. *See* 21 C.F.R. § 312.32, explaining that an adverse event may be categorized as "serious" if "in the view of either the investigator or sponsor, it results in any of the" listed outcomes.

10. Given that efficiency will be tracked for two years in this trial, it appears foolhardy to not also capture all adverse events during this period. If mRNA-1273 causes a systemic autoimmune issue to arise two months after vaccination, but that individual does not withdraw from the study (and why would they since they would have already received both doses of mRNA-1273), it would be irresponsible and unethical not to capture that reaction simply because the person did not withdraw from the trial.

b. Minimum Period to Track Adverse Events

11. At a minimum, all adverse events and reactions should be documented for each subject post-vaccination for at least: (i) twelve months for adults, (ii) thirty-six months for children, and (iii) sixty months for infants and toddlers. These minimal timeframes provide an opportunity to capture adverse and non-specific health issues that mRNA-1273 may cause.

12. The importance of capturing all potential health issues for a material duration can be seen in the designs of the clinical trials of numerous drugs, including for example, Enbrel[15], Lipitor[16], and Botox,[17] which had safety review periods of 6.6 years, 4.8 years, and 51 weeks respectively. As another example, the weight loss drug Belviq was safety tested for two years before being licensed by the FDA in 2012.[18] Nevertheless, despite this two year period, in February 2020 the drug was voluntarily removed from the US market due to emerging data that clinical trial participants had an increased occurrence of cancer five years later.[19]

13. The FDA states that the length of study for phase III clinical trials is typically "1 to 4 years"[20] and that the duration of a clinical trial should "reflect the product and target condition."[21] In accord with this guidance, and the fact that a COVID-19 vaccine will be an entirely novel product, the safety review period for adults should be at least 1 year. The need for this minimum safety review period following injection is further supported by the indications that the immunity

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[15] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503lbl.pdf (last visited August 11, 2020).

[16] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf (last visited August 11, 2020).

[17] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf (last visited August 11, 2020).

[18] *See* https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022529lbl.pdf (last visited August 11, 2020).

[19] *See* https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market (last visited August 11, 2020); *see also* https://www.health.harvard.edu/blog/weight-loss-drug-belviq-recalled-2020040919439 (last visited August 11, 2020).

[20] https://www.fda.gov/patients/drug-development-process/step-3-clinical-research (last visited August 11, 2020).

[21] https://www.fda.gov/media/102332/download (last visited August 11, 2020).

conferred by a COVID-19 vaccine is expected to last approximately one year or maybe a few years, requiring repeated injections of the product during a person's life.[22]

14. Moreover, taking into account the FDA's guidance that clinical trials should "reflect the product and target condition,"[23] the time frame for the safety review should be longer for minors, and in particular for babies and toddlers, since autoimmune, neurological, and developmental disorders will often not be diagnosed until after babies are at least a few years old.[24] Indeed, a 2019 review, authored by researchers at the FDA and Duke University, reviewed 306 pediatric clinical trials and found that short-term

> pediatric studies may not provide complete safety data across all critical periods of growth and development. This observation may be important because multiple periods of critical pediatric growth and development exist… Although the first 3 years of life are often considered more critical than older ages for brain development, biochemical studies of brain metabolism suggest that high brain metabolic rates characteristic of early childhood may not decline to adult levels until ages 16 to 18 years, suggesting that the school-age and adolescent periods are equally critical periods of brain development. Given this information, even the longest trial duration identified in our study (364 weeks/7 years) does not completely evaluate potential critical stages of all pediatric growth and development periods.[25]

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[22] The importance of the typical duration of a clinical trial was underscored by an AstraZeneca senior executive team member when he acknowledged the very real potential of side effects being discovered years down the line. In explaining why AstraZeneca needs protection from future product liability claims against its COVID-19 vaccine, Ruud Dobber stated: "This is a unique situation where we as a company simply cannot take the risk if in ... four years the vaccine is showing side effects." https://in.reuters.com/article/us-astrazeneca-results-vaccine-liability/astrazeneca-to-be-exempt-from-coronavirus-vaccine-liability-claims-in-most-countries-idINKCN24V2EN (last visited August 11, 2020).

[23] https://www.fda.gov/media/102332/download (last visited August 11, 2020).

[24] For example, according to the CDC, even for a common neurological disorder such as ADHD, "5 years of age was the average age of diagnosis for children reported as having severe ADHD." https://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html (last visited August 11, 2020). As another example, learning disabilities, a group of common developmental issues, are often "identified once a child is in school." https://www.nichd.nih.gov/health/topics/learning/conditioninfo/diagnosed (last visited August 11, 2020). Even for asthma, a very common autoimmune condition, whose symptoms are obvious, diagnosis can be difficult for children under 5 years of age because lung function tests aren't accurate before 5 years of age and "[s]ometimes a diagnosis can't be made until later, after months or even years of observing symptoms." https://www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/drc-20351513 (last visited August 11, 2020).

[25] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6526087/ (last visited August 11, 2020).

The FDA and Duke authors explained that, compared to licensing a drug for adults, "data on drug efficacy and safety in children may require an additional 6 years."[26] Since children have not been seriously affected by this virus, the risk of any vaccine must be fully understood in order to weigh it against any potential benefit.

c. Adequately Powered Sample Size

15. The study design for mRNA-1273 provides for only 30,000 individual study subjects, which presumably means only 15,000 individuals will be in the study group that will receive mRNA-1273 and 15,000 individuals will be in the control group that will receive a placebo.

16. A Phase III trial of this size for mRNA-1273 cannot produce an adequate safety profile for this product. SARS-CoV-2 poses a statistically insignificant risk of harm to children and young healthy adults. For this enormous cohort of the American population, the threshold for establishing that this vaccine is safer than the infection is exceedingly high and requires a highly powered trial. Even within so-called higher risk groups, the percent of individuals suffering serious health issues from SARS-CoV-2 is statistically small on a population level, which again demands a well-powered trial to assess the safety of the vaccine versus natural infection, since it is anticipated that this vaccine will be mandatory for most Americans.

17. Reflecting the foregoing, even Dr. Paul Offit, a member of VRBPAC and a staunch advocate for removing hurdles to the licensure of vaccines, has said that to determine whether a COVID-19 vaccine is safe and effective, "we are waiting for the big trial … the large prospective placebo controlled trial, we have 20,000 people who get a vaccine, 10,000 people who get a placebo, then and only then will you know whether a vaccine is safe and effective."[27] But even 20,000 subjects in the group receiving the experimental vaccine may not be sufficient according to the a report from the Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, FDA, with regard to assessing the safety of mRNA-1273 for anyone other than the groups with the highest risk of complications from SARS-CoV-2.[28]

18. The study, then, must use an adequate sample size, appropriately powered, in order to (i) detect an increase in rare adverse events or, any untoward medical occurrence, whether or not considered vaccine related and (ii) determine that the rate of adverse events from the vaccine will not exceed the rate of adverse events known to occur from SARS-CoV-2 in the group under review.

d. T-cell Reactivity and Response

19. Clinical trials participants should be tested for T-cell reactivity to SARS-CoV-2 prior to vaccination and then again after vaccination.

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[26] *Id*.

[27] https://www.cnn.com/videos/health/2020/05/24/coronavirus-covid-19-vaccine-trials-vaccinologist-concern-ip-vpx.cnn (emphasis added) (last visited August 11, 2020).

[28] *See* https://pubmed.ncbi.nlm.nih.gov/11802587/ (last visited August 11, 2020).

20. This is necessary because, as recently explained in the journal Nature Reviews Immunology by researchers from the Center for Infectious Disease and Vaccine Research at La Jolla Institute for Immunology, "if subjects with pre-existing reactivity were sorted unevenly in different vaccine dose groups, this might lead to erroneous conclusions. Obviously, this could be avoided by considering pre-existing immunity as a variable to be considered in trial design."[29]

21. Dr. Sette, a member of this group, further explained that "if you have 10 people that have reactivity and 10 people that don't have the pre-existing reactivity and you vaccinate them with a SARS CoV-2 vaccine, the ones that have the pre-existing immunity will respond faster or better to a vaccine ... So, we have been suggesting to anybody that is running vaccine trials to also measure T-cell response."[30]

C. ENVIRONMENTAL IMPACT

22. The undersigned 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.

D. ECONOMIC IMPACT

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

E. CERTIFICATION

24. 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.

25. The Petitioner therefore respectfully urges that this request be granted forthwith.

Respectfully submitted,

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[29] https://www.nature.com/articles/s41577-020-0389-z (last visited August 11, 2020).

[30] https://amp.cnn.com/cnn/2020/08/02/health/gupta-coronavirus-t-cell-cross-reactivity-immunity-wellness/index.html (last visited August 11, 2020).

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