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VIA ELECTRONIC FILING

November 6, 2020

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
Commissioner Stephen M. Hahn, M.D.
5630 Fishers Lane
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UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES AND THE FOOD AND DRUG ADMINISTRATION

PETITION FOR ADMINISTRATIVE ACTION REGARDING EFFICACY END POINTS OF THE PHASE III CLINICAL TRIALS OF COVID-19 VACCINES	**:**	**Docket No._____**

CITIZEN PETITION

This petition for administrative action is submitted on behalf of Informed Consent Action Network[1] ("**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 Phase III trials of mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722) conform with the requests in the "Actions Requested" section below before licensure.

Because of the compelling need to ensure the 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 by November 20, 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 trials of mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722)[2] be amended to provide that:

a. reduction in severe COVID-19 (*i.e.*, hospital admissions, ICU admissions, and death) be a primary endpoint;

b. PCR tests used to qualify an event of COVID-19 for a trials' endpoint use a maximum of 24 amplification cycles;

c. interruption of transmission (person-to-person spread) be a primary endpoint; and

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

B. STATEMENT OF GROUNDS[3]

2. The current study designs for the Phase III clinical trials for mRNA-1273 ("**the Moderna Vaccine**"),[4] BNT162 ("**the Pfizer Vaccine**"),[5] AZD1222 ("**the AstraZeneca Vaccine**"),[6] and Ad26.COV2.S ("**the Johnson & Johnson Vaccine**")[7] (collectively, "**the COVID-19 Vaccines"**) are inadequate to assess efficacy.

3. Petitioner will suffer irreparable harm if the actions requested herein are 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 issued a report on COVID-19 recommending that, "a vaccine subject to scientific evidence of safety and efficacy be made widely available, and widely encouraged, and if the public health authorities conclude necessary, required…"[8] Hence, without the FDA assuring proper efficacy trials of the vaccine *now*, the

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[2] NCT04470427 available at https://www.clinicaltrials.gov/ct2/show/NCT04470427; NCT04368728 available at https://www.clinicaltrials.gov/ct2/show/NCT04368728; NCT04516746 available at https://www.clinicaltrials.gov/ct2/show/NCT04516746; NCT04505722 available at https://www.clinicaltrials.gov/ct2/show/NCT04505722 (last visited November 3, 2020).

[3] 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 November 3, 2020).

[4] Moderna/NIAID clinical trial protocol (last visited November 3, 2020).

[5] BioNTech/Pfizer clinical trial protocol (last visited November 3, 2020).

[6] Oxford/AstraZeneca Vaccine clinical trial protocol (last visited November 3, 2020).

[7] Johnson & Johnson clinical trial protocol (last visited November 3, 2020).

[8] https://nysba.org/app/uploads/2020/09/Health-Law-Section-COVID-19-Report-September-20-2020.pdf (last visited November 3, 2020).

Petitioner will not have the opportunity to object to receiving the vaccine based on deficient clinical trials *later*.

4. Furthermore, if the vaccine is licensed without an appropriate efficacy review, then any potential acceptance or mandate of these vaccines are likely to be based on inaccurate beliefs about the vaccine, namely that it will stop transmission of the virus from the vaccine recipient to others or that it will reduce severe COVID-19 disease and deaths. The trial protocols are not currently designed to determine whether either of those objectives can be met.

5. The public interest also weighs strongly in favor of the requested relief because improving primary endpoints to prove a reduction in serious disease, hospitalizations, death and blocking of transmission and T-cell testing (i) will comport with the best scientific practices, (ii) increase public confidence in the efficacy of a product expected to be mandated, and (iii) not doing so will have the opposite result in that it will create uncertainties regarding the efficacy of and need for the COVID-19 vaccines.

a. Reduction in Severe COVID-19 (Including Hospital Admissions, ICU Admissions, and Death) Should Be a Primary Endpoint of the Clinical Trials

6. To increase assurance that the COVID-19 Vaccines will effectively reduce severe disease and death, reduction in severe COVID-19, including hospital admissions, ICU admissions, and death) should be a primary endpoint of the COVID-19 Vaccine clinical trials.

7. Despite what the general public may believe, the COVID-19 Vaccine trials are not currently designed to detect any improvement in severe cases of COVID-19, hospitalizations, or deaths. Instead, the trials will capture any mild COVID-19 cases and seek approval and/or licensure based on same.

8. The trials' primary endpoints include prevention of symptomatic disease in the vaccine recipient. In order to evaluate that endpoint, each trial will track recorded "events" of COVID-19 disease. However, the threshold to meet the criteria of such an "event" is exceedingly low. [9] In the Moderna and Pfizer trials, for example, if a participant has a positive polymerase chain reaction ("**PCR**") test along with a cough, that participant would be counted as an "event." For AstraZeneca's trial, if a participant has a positive PCR test, a cough, and fever, this too would count as a qualifying event. Once a trial reaches a certain number of "events", the trial is closer to seeking FDA approval or licensure by demonstrating that the vaccines is "effective" (in that the vaccine group had lower incidence of events than the control group).

9. AstraZeneca's trial protocol defines the primary endpoint as "the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention." Participants will be included in the primary endpoint if they have a positive PCR test and meet the following criteria at any point from their initial illness visit at the site through their second illness visit:

[9] *See* notes 4-7*, supra*.

1 One or more Category A findings

OR

2 Two or more Category B findings

Category A:

- Pneumonia diagnosed by chest x-ray, or computed tomography scan
- Oxygen saturation of ≤ 94% on room air or requiring either new initiation or escalation in supplemental O2
- New or worsening dyspnea/shortness of breath

Category B:

- Fever > 100 °F (> 37.8 °C) or feverishness
- New or worsening cough
- Myalgia/muscle pain
- Fatigue that interferes with activities of daily living
- Vomiting and/or diarrhea (only one finding to be counted toward endpoint definition)
- Anosmia and/or ageusia (only one finding to be counted toward endpoint definition).[10]

10. These thresholds will result in mild cases of COVID-19 being considered as events. If a participant with a positive PCR has fatigue and feverishness, this is considered symptomatic illness with COVID-19.

11. Notably, if an individual has a positive PCR test and an oxygen saturation of 94% or less, this is an event. However, in 1 out of 20 asymptomatic, community-dwelling adults age 65 years or older, an oxygen saturation level of less than or equal to 92% is normal.[11] In that instance, a trial participant would simply need a positive PCR test to be considered a qualifying event. An oxygen saturation level of 94% may capture a completely asymptomatic or healthy individual.

12. The Johnson & Johnson protocol represents that for the primary endpoint, "all moderate and severe/critical COVID-19 cases will be considered." However, "moderate" COVID-19 is determined with a positive PCR test and:

[10] *See* n. 6, *supra*.

[11] *See* https://onlinelibrary.wiley.com/doi/full/10.1111/jgs.12580 (last visited November 3, 2020).

Any 1 of the following new or worsening signs or symptoms:		Any 2 of the following new or worsening signs or symptoms:
• Respiratory rate ≥20 breaths/minute • Abnormal saturation of oxygen (SpO_2) but still >93% on room air at sea level* • Clinical or radiologic evidence of pneumonia • Radiologic evidence of deep vein thrombosis (DVT) • Shortness of breath or difficulty breathing	**OR**	• Fever (≥38.0°C or ≥100.4°F) • Heart rate ≥90 beats/minute • Shaking chills or rigors • Sore throat • Cough • Malaise as evidenced by 1 or more of the following**: - Loss of appetite - Generally unwell - Fatigue - Physical weakness • Headache • Muscle pain (myalgia) • Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)** • New or changing olfactory or taste disorders • Red or bruised looking feet or toes

[12]

13. Just as in the AstraZeneca trial, the oxygen saturation level is not adequate to capture a symptomatic individual and must be lowered. Otherwise, far from capturing "moderate" cases of COVID-19, the trial will potentially capture a normal, asymptomatic individual aged 65 or older with a typical lower oxygen saturation level. Similarly, if a trial participant has a positive PCR test along with a fever and headache, that is considered a "moderate" case of COVID-19 in the Johnson & Johnson trial.

14. The Moderna protocol is similarly inadequate. That protocol captures all COVID-19 events which are defined as "symptomatic disease based on the following criteria:"

> • The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38oC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s),
> OR
> • The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia;
> AND
> • The participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.[13]

15. If a Moderna trial participant has a positive PCR test along with a cough, that will be classified as a COVID-19 event.

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[12] *See* n. 7, *supra*.

[13] *See* n. 4, *supra*.

16. Pfizer's trial suffers the same issues. The protocol's primary endpoint calls for "Confirmed COVID" which is defined as "presence of at least 1 of the following symptoms" and a SARS-CoV-2positive test" and it then lists:

- Fever
- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste or smell
- Sore throat
- Diarrhea
- Vomiting[14]

17. Here, a positive PCR test and a sore throat will qualify as a "confirmed COVID-19" event.

18. As the trials currently stand, this effectively means that the efficacy of the vaccine will potentially (and likely) be evaluated based on only mild cases of the disease (if on the disease at all). This will not shed light on any vaccine's ability to reduce or stop severe disease, hospitalization, or death. It will only inform the public whether or not the vaccine can prevent mild symptoms such as a fever, cough, or sore throat.

19. To the extent there is concern that there is not enough severe cases of or death from COVID-19 to make these an endpoint, then the situation with this virus is not critical enough to allow for lower efficacy standards. Clinical trials that only have mild cases of COVID-19 as an endpoint will result in a vaccine that is potentially ineffective at preventing what the public is and what the FDA should be concerned about – severe cases and death from SARS-CoV-2.

b. PCR tests used to qualify an event of COVID-19 for trials' endpoints use a maximum of 24 amplification cycles

20. There are serious issues associated with the trials' use of the PCR test as the linchpin in determining whether a participant has COVID-19 disease. PCR tests are qualitative

[14] *See* n. 5*, supra*.

and not quantitative.[15] They are not standardized.[16] They have an incredibly high rate of false positives and even a positive result does not mean an individual can infect others.[17] The trials must account for these facts. They must require that COVID-19 cases are only classified as such when participants are symptomatic and suffering with at least moderate to severe COVID-19.

21. The number of PCR cycles it takes to amplify a sample containing viral remains to the point where they can be detected is called its cycle threshold. If PCR tests are going to be used in the COVID-19 Vaccine trials to identify cases of COVID-19, then the cycle threshold must be set at a reasonable number.

22. Dr. Anthony Fauci, when asked about transmission and testing, has explained this serious issue with PCR tests as follows: "What is now sort of evolving into a bit of a standard that if you get a cycle threshold of 35 or more, that the chances of it being replication competent are minuscule…you almost never can culture virus from a 37 threshold cycle so…if somebody does come in with 37, 38, even 36, you gotta' say, you know, it's just dead nucleotides, period."[18]

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[15] *See* https://www.nytimes.com/2020/08/29/health/coronavirus-testing.html ("The most widely used diagnostic test for the new coronavirus, called a PCR test, provides a simple yes-no answer to the question of whether a patient is infected… 'We've been using one type of data for everything, and that is just plus or minus — that's all,' Dr. Mina said. 'We're using that for clinical diagnostics, for public health, for policy decision-making.' But yes-no isn't good enough, he added. It's the amount of virus that should dictate the infected patient's next steps. 'It's really irresponsible, I think, to forgo the recognition that this is a quantitative issue,' Dr. Mina said.") (last visited November 3, 2020).

[16] *See Understanding cycle threshold (CT) in SARS-CoV-2 RT-PCR* at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/926410/Understanding_Cycle_Threshold__Ct__in_SARS-CoV-2_RT-PCR_.pdf ("Cycle threshold (Ct) is a semi-quantitative value that can broadly categorise the concentration of viral genetic material in a patient sample following testing by RT PCR as low, medium or high – that is, it tells us approximately how much viral genetic material is in the sample… Ct values cannot be directly compared between assays of different types – not all laboratories use the same assay, and some may use more than one.") (last visited November 3, 2020); *see also* https://www.nytimes.com/2020/08/29/health/coronavirus-testing.html ("The Food and Drug Administration said in an emailed statement that it does not specify the cycle threshold ranges used to determine who is positive, and that 'commercial manufacturers and laboratories set their own.'") (last visited November 3, 2020).

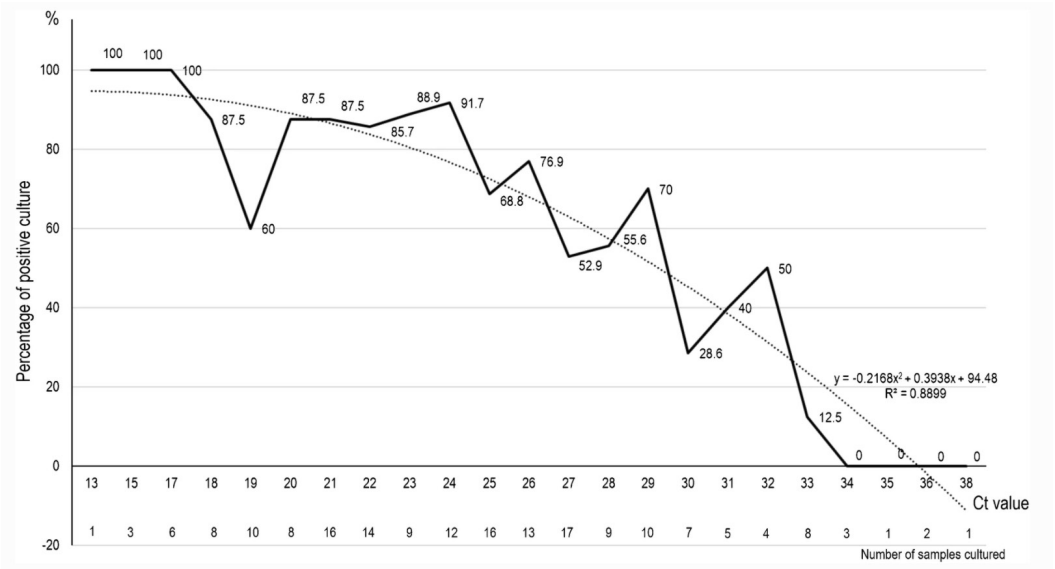
[17] *See* https://www.nytimes.com/2020/08/29/health/coronavirus-testing.html ("In three sets of [PCR] testing data that include cycle thresholds, compiled by officials in Massachusetts, New York and Nevada, up to 90 percent of people testing positive carried barely any virus, a review by The Times found…Any test with a cycle threshold above 35 is too sensitive, agreed Juliet Morrison, a virologist at the University of California, Riverside. 'I'm shocked that people would think that 40 could represent a positive,' she said. A more reasonable cutoff would be 30 to 35, she added. Dr. Mina said he would set the figure at 30, or even less.") (last visited November 3, 2020). Importantly, in discussing PCR testing in the context of pertussis, the CDC warns that "[t]he high sensitivity of PCR increases the risk of false-positivity."). *See* https://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-confirmation.html (last visited November 3, 2020).

[18] *See* https://www.youtube.com/watch?v=a_Vy6fgaBPE&feature=youtu.be&t=230 (last visited November 3, 2020).

23. According to the CDC's data, it is extremely difficult to detect *any* live virus in a sample above a threshold of 33 cycles.[19] One study that the CDC relied upon reports finding no "live" virus in any samples whose cycle threshold is greater than 24.[20] *All* studies that the CDC relied upon were conducted on symptomatic people.

24. Moreover, an analysis of several different studies by a team at Oxford similarly concluded that positive PCR test results from samples with cycle thresholds over 24 should not be taken to indicate the presence of any actual virus. This study concluded that, "[a] binary Yes/No approach to the interpretation RT-PCR unvalidated against viral culture will result in false positives with possible segregation of large numbers of people who are no longer infectious and hence not a threat to public health."[21]

25. This figure shows the significant relationship between cycle threshold value and culture positivity rate:



Percentage of positive viral culture of SARS-CoV-2 PCR-positive nasopharyngeal samples from Covid-19 patients, according to Ct value (plain line). The dashed curve indicates the polynomial regression curve[22]

26. The figure shows that a cycle threshold value of 35 means 10% positive cultures (or 90% negative cultures) for COVID-19. In order to have at least a 50% chance of a positive culture, a PCR test should be at or lower than 30 amplification cycles. The study further concluded

[19] *See* https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html (last visited November 3, 2020).

[20] *See* https://pubmed.ncbi.nlm.nih.gov/32442256/ ("SARS-CoV-2 Vero cell infectivity was only observed for RT-PCR Ct < 24.") (last visited November 3, 2020).

[21] https://www.medrxiv.org/content/10.1101/2020.08.04.20167932v4.full.pdf (last visited November 3, 2020).

[22] *See* https://link.springer.com/article/10.1007/s10096-020-03913-9 (last visited November 3, 2020).

that "patients with Ct [cycle threshold] values equal or above 34 do not excrete infectious viral particles."

27. The COVID-19 Vaccine trial protocols do not disclose the cycle thresholds being used for the PCR tests in order to assess the primary endpoints. These cycle thresholds must not be higher than 24.

c. Interruption of Transmission (Person-to-person Spread)

28. Again, despite what the general public may believe, the COVID-19 Vaccine trials are not currently designed to analyze whether or not the vaccines will prevent transmission of the virus from one individual to others.

29. On top of only offering insight as to a vaccine's effect on mild disease, the clinical trials also do not call for interruption of transmission of the disease as a primary endpoint – what should arguably be the most important endpoint. This means that, aside from an individual choosing to take the vaccine in order to protect him/herself from mild COVID-19, there may be no potential benefit to the larger population, or at the very least the studies currently underway will not tell us whether the vaccines truly do prevent transmission.

30. This is similar to the pertussis vaccine which offers a reduction in symptoms for vacinees who become infected with pertussis but does not offer protection from infection nor does it prevent vacinees from transmitting pertussis to others.[23] The fact that a vaccine may lessen the severity of symptoms in a recipient (and be considered "effective" for that measure alone) cannot be confounded with its ability to prevent infection and transmission.

31. The Chief Medical Officer at Moderna, Tal Zaks, openly admitted that the "trial will not demonstrate prevention of transmission."[24] When speaking with *The BMJ*, Zaks explained that "in order to [demonstrate prevention of transmission] you have to swab people twice a week for very long periods and that becomes operationally untenable."[25]

32. As Peter Doshi, Associate Editor at *The BMJ*, further reported: "COVID-19 vaccine trials are currently designed to tabulate final efficacy results once 150 to 160 trial participants develop symptomatic COVID-19 – and most trials have specified at least one interim analysis allowing for the trials to end with even fewer data accrued."[26] Eric Topol, from Medscape, criticized this procedure, saying: "These numbers seem totally out of line with what would be

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[23] *See* https://pubmed.ncbi.nlm.nih.gov/31333640/ ("Consequently, preventive measures such as aPVs [acellular pertussis vaccines] that do not induce a valid mucosal response can prevent disease but cannot avoid infection and transmission.") (last visited November 3, 2020).

[24] https://www.bmj.com/content/371/bmj.m4037 (last visited November 3, 2020).

[25] *Id*.

[26] *Id*.

considered stopping rules…you're talking about giving a vaccine with any of these programmes to tens of millions of people. And you're going to base that on 100 events?"[27]

33. As Peter Hotez, dean of the National School of Tropical Medicine at Baylor College of Medicine in Houston, said: "Ideally, you want an antiviral vaccine to do two things…first, reduce the likelihood you will get severely ill and go to the hospital, and two, prevent infection and therefore interrupt disease transmission."[28] The four frontrunner COVID-19 Vaccines' Phase III trial protocols do not analyze, and certainly do not guarantee, either of those things and they should be required to do so.

d. T-cell Reactivity and Response

34. All clinical trial participants should be tested for T-cell reactivity to SARS-CoV-2 prior to vaccination and then again after vaccination.

35. This is necessary because, as recently explained in the journal Nature Reviews Immunology, by researchers at 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]

36. 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

37. 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

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

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[27] *Id*.

[28] https://www.msn.com/en-us/health/medical/those-coronavirus-vaccines-leading-the-race-don-t-ditch-the-masks-quite-yet/ar-BB17mN6n (last visited November 3, 2020).

[29] https://www.nature.com/articles/s41577-020-0389-z (last visited November 3, 2020).

[30] https://amp.cnn.com/cnn/2020/08/02/health/gupta-coronavirus-t-cell-cross-reactivity-immunity-wellness/index.html (last visited November 3, 2020).

E. CERTIFICATION

39. 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.

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

Respectfully submitted,

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