December 11, 2020

Aaron Siri
Siri & Glimstad LLP
200 Park Avenue
17th Floor
New York, NY 10166

Re: Citizen Petition and Petition for Administrative Stay of Action (Docket Number FDA-2020-P-2180)

Dear Mr. Siri,

This letter responds to the following citizen petition and petition for administrative stay of action that you submitted to the Food and Drug Administration (FDA, the Agency, we) on behalf of Informed Consent Action Network (Petitioner) relating to Phase 3 trials of certain vaccines to prevent the novel coronavirus SARS-CoV-2 (COVID-19):

- The citizen petition dated November 6, 2020 (the CP); and
- The petition for administrative stay of action dated November 11, 2020 (the PSA)

(collectively, the Petitions).[1]

In the CP, Petitioner requests FDA to amend "the study design for the Phase III trials of mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722)" 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.

CP at 2.

In the PSA, Petitioner requests FDA to:

[1] FDA has also received the petitions that you submitted on behalf of ICAN regarding clinical trials of vaccines to prevent COVID-19 in the following dockets: FDA-2020-P-1601, FDA-2020-P-1768, FDA-2020-P-1769, FDA-2020-P-1770, and FDA-2020-P-2096. FDA is responding separately to those petitions.

Stay the Phase III trials of mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722) until their study designs are 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.

PSA at 2.

This letter responds to the CP and the PSA in full. We have carefully considered the information submitted in the Petitions, comments submitted to the docket, and other information available to the Agency. Based on our review of these materials and for the reasons described below, we conclude that the Petitions do not contain facts demonstrating any reasonable grounds for the requested action. In accordance with 21 CFR §§ 10.30(e)(3) and 10.35(e), and for the reasons stated below, FDA is denying the Petitions.

I. Background

There is currently a pandemic of respiratory disease, Coronavirus Disease 2019 (COVID-19), caused by a novel coronavirus, SARS-CoV-2. The COVID-19 pandemic presents an extraordinary challenge to global health. On January 31, 2020, the Secretary of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19.[2] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[3] There are currently no FDA-licensed vaccines to prevent COVID-19. Commercial vaccine manufacturers and other entities are developing COVID-19 vaccine candidates, and clinical studies of these vaccines are underway.

II. Vaccines that are FDA-Licensed or Receive an Emergency Use Authorization Meet Relevant Statutory Requirements

A. Licensed Vaccines

FDA has a stringent regulatory process for licensing vaccines.[4,5] The Public Health Service Act (PHS Act) authorizes FDA to license biological products, including vaccines, if they have

[2] Secretary of HHS Alex M. Azar, Determination that a Public Health Emergency Exists, originally issued January 31, 2020, and subsequently renewed, https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.
[3] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak, issued March 13, 2020, https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.
[4] CDC, Ensuring the Safety of Vaccines in the United States, February 2013, https://www.cdc.gov/vaccines/hcp/patient-ed/conversations/downloads/vacsafe-ensuring-bw-office.pdf.
[5] Vaccine Safety Questions and Answers, lasted updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.

been demonstrated to be "safe, pure, and potent."[6] As is evident from the language of the PHS Act and FDA's regulations, the licensure process for a vaccine requires the sponsor to establish, through carefully controlled laboratory and clinical studies, as well as through other data, that the product is safe and effective for its approved indication(s) and use. FDA's multidisciplinary review teams then rigorously evaluate the sponsor's laboratory and clinical data, as well as other information, to help assess whether the safety, purity, and potency of a vaccine has been demonstrated.[7] FDA regulations explicitly state that "[a]pproval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products."[8] Only when FDA's standards are met is a vaccine licensed.

For more information on FDA's thorough process for evaluating vaccines, see Appendix I of this letter, *Aspects of Vaccine Development and Process for Licensure*.

B. Emergency Use Authorization

Congress established the Emergency Use Authorization (EUA) pathway to ensure that, during public health emergencies, potentially lifesaving medical products could be made available before being approved. The EUA process allows the Secretary of HHS, in appropriate circumstances, to declare that EUAs are justified for products to respond to certain types of threats. When such a declaration is made, FDA may issue an EUA, which is different from the regulatory process for vaccine licensure.

Section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 360bbb-3) authorizes FDA to, under certain circumstances, issue an EUA to allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by chemical, biological, radiological, or nuclear threat agents when there are no adequate, approved, and available alternatives. On February 4, 2020, pursuant to section 564(b)(1)(C) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)(C)), the Secretary of HHS determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19.[9] On the basis of such determination, on March 27, 2020, the Secretary of HHS then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564(b)(1) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)).[10]

Based on this declaration and determination, under section 564(c) of the FD&C Act (21 U.S.C. § 360bbb-3(c)), FDA may issue an EUA during the COVID-19 pandemic after FDA concludes that the following statutory requirements are met:

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[6] See 42 U.S.C. § 262(a)(2)(C)(i)(I).
[7] Vaccines, last updated June 2020, https://www.fda.gov/vaccines-blood-biologics/vaccines.
[8] See 21 CFR § 601.2(d).
[9] 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[10] 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

- The agent referred to in the March 27, 2020, EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.

- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.

- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

Although EUAs are governed under a different statutory framework than a Biologics License Application (BLA), FDA has made clear that issuance of an EUA for a COVID-19 vaccine would require that the vaccine demonstrated clear and compelling safety and efficacy in a large, well-designed Phase 3 clinical trial. In the guidance document entitled Emergency Use Authorization for Vaccines to Prevent COVID-19 (October 2020 Guidance), FDA has provided recommendations that describe key information that would support issuance of an EUA for a vaccine to prevent COVID-19.[11] In the October 2020 Guidance, FDA explained that, in the case of such investigational vaccines, any assessment regarding an EUA will be made on a case-by-case basis considering the target population, the characteristics of the product, the preclinical and human clinical study data on the product, and the totality of the available scientific evidence relevant to the product.[12] FDA has also stated, in the October 2020 Guidance, that for a COVID-19 vaccine for which there is adequate manufacturing information to ensure its quality and consistency, issuance of an EUA would require a determination by FDA that the vaccine's benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial that demonstrates the vaccine's safety and efficacy in a clear and compelling manner.[13]

- A Phase 3 trial of a vaccine is generally a large clinical trial in which a large number of people are assigned to receive the investigational vaccine or a control. In general, in Phase 3 trials that are designed to show whether a vaccine is effective, neither people receiving the vaccine nor those assessing the outcome know who received the vaccine or the comparator.

- In a Phase 3 study of a COVID-19 vaccine, the efficacy of the investigational vaccine to prevent disease will be assessed by comparing the number of cases of disease in each study group. For Phase 3 trials, FDA has recommended to manufacturers in guidance that the vaccine should be at least 50% more effective than the comparator, and that the outcome

[11] Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry, October 2020, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19.
[12] Id. at 3.
[13] Id. at 4.

be reliable enough so that it is not likely to have happened by chance.[14] During the entire study, subjects will be monitored for safety events. If the evidence from the clinical trial meets the pre-specified criteria for success for efficacy and the safety profile is acceptable, the results from the trial can potentially be submitted to FDA in support of an EUA request.

Several investigational COVID-19 vaccines are now being studied in Phase 2 or Phase 3 trials. Following clinical trials, manufacturers analyze data prior to submitting to FDA a BLA to request approval from FDA to market the vaccine. A BLA for a new vaccine includes information and data regarding the safety, effectiveness, chemistry, manufacturing and controls, and other details regarding the product. The goal timelines for FDA's comprehensive BLA review and evaluation are detailed in the Prescription Drug User Fee Act (PDUFA) goals letter and range from 6 – 10 months after the application has been filed.[15] During the current public health emergency, manufacturers may, with the requisite data and taking into consideration input from FDA, choose to submit a request for an EUA.

It is FDA's expectation that, following submission of an EUA request and issuance of an EUA, a sponsor would continue to evaluate the vaccine and would also work towards submission of a BLA as soon as possible.

III. Discussion

The Petitions pertain to "[t]he current study designs for the Phase III clinical trials for mRNA-1273 ('the Moderna Vaccine'),[] BNT162 ('the Pfizer Vaccine'),[] AZD1222 ('the AstraZeneca Vaccine'),[] and Ad26.COV2.S ('the Johnson & Johnson Vaccine')[] (collectively, 'the COVID-19 Vaccines')." FDA's investigational new drug process applies to the development and approval of new drugs and biological products, including vaccines.[16]

A. Investigational New Drugs

Before a vaccine is licensed (approved) by FDA for use by the public, FDA requires that it undergo a rigorous and extensive development program to determine the vaccine's safety and effectiveness. This development program encompasses preclinical research (laboratory research, animal studies[17]) and clinical studies. At the preclinical stage, the sponsor focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies. Clinical studies, in humans, are conducted under well-defined conditions and with careful safety monitoring through all the

[14] Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry, June 2020 (June 2020 Guidance), https://www.fda.gov/media/142749/download.
[15] PDUFA Reauthorization Performance Goals And Procedures Fiscal Years 2018 Through 2022; https://www.fda.gov/media/99140/download.
[16] See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).
[17] We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

phases of the investigational new drug application (IND) process. FDA's regulations governing the conduct of clinical investigations are set out at 21 CFR Part 312.

Before conducting a clinical investigation in the United States in which a new drug or biological product is administered to humans, a sponsor must submit an IND to FDA.[18] The IND describes the proposed clinical study in detail and, among other things, helps protect the safety and rights of human subjects.[19] In addition to other information, an IND must contain information on clinical protocols and clinical investigators. Detailed protocols for proposed clinical studies permit FDA to assess whether the initial-phase trials will expose subjects to unnecessary risks. Information on the qualifications of clinical investigators (professionals, generally physicians, who oversee the administration of the experimental drug) permits FDA to assess whether they are qualified to fulfill their clinical trial duties. The IND includes commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB),[20] and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials, unless FDA informs the sponsor that the trial may begin earlier. During this time, FDA reviews the IND. FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and Phase 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.[21]

FDA's regulations provide that, once an IND is in effect, the sponsor may conduct a clinical investigation of the product, with the investigation generally being divided into three phases. With respect to vaccines, the initial human studies, referred to as Phase 1 studies, are generally safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase 2 studies may include up to several hundred individuals and are designed to provide information regarding the incidence of common short-term side effects such as redness and swelling at the injection site or fever and to further describe the immune response to the investigational vaccine. If an investigational new vaccine progresses past Phase 1 and Phase 2 studies, it may progress to Phase 3 studies. For Phase 3 studies, the sample size is often determined by the number of subjects required to establish the effectiveness of the new vaccine, which may be in the thousands or tens of thousands of subjects. Phase 3 studies provide the critical documentation of effectiveness and important additional safety data required for licensing.

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[18] See 21 CFR § 312.20(a).

[19] For additional information regarding the IND review process and general responsibilities of sponsor-investigators related to clinical investigations see Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators; Draft Guidance for Industry, May 2015, https://www.fda.gov/media/92604/download.

[20] The IRB is a panel of scientists and non-scientists in hospitals and research institutions that oversees clinical research. IRBs approve clinical study protocols, which describe the type of people who may participate in the clinical study; the schedule of tests and procedures; the medications and dosages to be studied; the length of the study; the study's objectives; and other details. IRBs make sure that the study is acceptable, that participants have given consent and are fully informed of the risks, and that researchers take appropriate steps to protect patients from harm. See The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective, last updated November 2017, https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.

[21] See 21 CFR § 312.22(a).

At any stage of development, if data raise significant concerns about either safety or effectiveness, FDA may request additional information or studies; FDA may also halt ongoing clinical studies. The FD&C Act provides a specific mechanism, called a "clinical hold," for prohibiting sponsors of clinical investigations from conducting the investigation (section 505(i)(3) of the FD&C Act; 21 U.S.C. § 355(i)(3)), and FDA's IND regulations in 21 CFR § 312.42 identify the circumstances that may justify a clinical hold. Generally, a clinical hold is an order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or to suspend an ongoing investigation. 21 CFR § 312.42(a).

B. The Citizen Petition

The Petitioner requests that FDA "amend" the "study design for the Phase III trials of mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722)" to include certain design characteristics. CP at 2. Because FDA does not itself create or amend drug investigations,[22] we interpret the CP as asking that FDA require the sponsors to make the requested changes.[23] As explained above, with certain exceptions, clinical investigations in which a drug is administered to human subjects must be conducted under an IND submitted to FDA by the sponsor. FDA's review of an IND includes a review of the study protocol which describes, among other things, the design of the clinical study, including the identified endpoints and methods for assessing the effectiveness of the investigational product.

Below we discuss the requested changes to the study designs.

1. Reduction in Severe COVID-19 Be a Primary Endpoint

Petitioner requests FDA to amend the Phase 3 trials of the COVID-19 Vaccines' study design to provide that "reduction in severe COVID-19 (i.e., hospital admissions, ICU admissions, and death) be a primary endpoint." CP at 2. Specifically, Petitioner asserts that the primary end points in the Phase 3 clinical trial study designs "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." CP at 3. Petitioner also notes that:

> 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).

CP at 3.

Petitioner further asserts:

[22] Rather, sponsors are responsible for the designs of the clinical studies. FDA reviews INDs and may place INDs on clinical holds pursuant to 21 CFR § 312.42 if the Agency identifies certain deficiencies.

[23] To the extent the Petitioner asks for FDA to itself amend a sponsor's investigational study design, we deny the Petition because that is not FDA's role with respect to the clinical trials.

> 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.

CP at 6.

We do not agree that in order to demonstrate the effectiveness of an investigational COVID-19 vaccine sponsors must limit the primary efficacy analysis to an assessment of cases of severe COVID-19. Vaccine development has a long history, and we are not aware of an example of any vaccine that is effective against mild disease that is not also effective against severe disease. Furthermore, given that severe cases of COVID-19 occur less frequently than mild-to-moderate cases, trials designed to use the incidence of severe COVID-19 as the primary endpoint would require a higher number of study participants and take a longer time to conduct.

You maintain that "[t]o 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." CP at 6. However, we do not agree. The COVID-19 pandemic is a public health emergency. In any case, we do not view our position as accepting "lower efficacy standards." Given that vaccines that have been shown to prevent mild disease have historically been shown to prevent severe disease, and given the practical concerns with designing clinical trials to measure effectiveness at reducing severe COVID-19 as a primary objective, we believe it is in the public interest to consider the results of vaccine trials that measure effectiveness based on reducing COVID-19—and not just severe COVID-19. Furthermore, we do not interpret the applicable statutory standards for licensure or authorization as requiring vaccine efficacy trials to evaluate incidence of severe COVID-19 as the primary endpoint.

Additionally, while we disagree with Petitioner's request to amend the study designs to require "severe COVID-19" as the primary endpoint, the Agency nevertheless intends to consider all the data from these studies, which we would expect would include data for cases varying in severity (including severe disease), to make our benefit-risk determination. We note that the public health is best served by FDA using our science-based decision-making process, including our determination that the effectiveness of a vaccine can be shown by measuring reduction of symptomatic COVID-19, to assure that any vaccine for COVID-19 that is authorized or approved meets the relevant statutory standards for safety and effectiveness.

2. PCR tests Use a Maximum of 24 Amplification Cycles

Petitioner also requests that the Agency require that, for the Phase 3 trials that involve the use of PCR tests, the "PCR tests used to qualify an event of COVID-19 for a trials' endpoints use a maximum of 24 amplification cycles." CP at 6. The Petitioner states that "[t]here are serious issues associated with the trials' use of the PCR test as the linchpin in determining whether a participant has COVID-19 disease," and that the trials "must account" for the fact that PCR tests have "an incredibly high rate of false positives." CP at 6-7. With respect to the amplification cycle request, Petitioner states that 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" and that such a threshold "must be set at a reasonable number." CP at 7.[24]

FDA agrees that accurate testing is an important part of ensuring the reliability of vaccine trial outcomes. An accurate test helps confirm whether the investigational vaccine prevents COVID-19 (or not) by confirming whether study participants are infected with SARS-CoV-2. Indeed, FDA's June 2020 Guidance states that "[d]iagnostic assays used to support the pivotal efficacy analysis (e.g., RT-PCR) should be sensitive and accurate for the purpose of confirming infection and should be validated before use."[25]

However, we disagree that it is necessary to require a maximum of 24 amplification cycles for PCR tests. PCR tests are used to show if individuals have active SARS-CoV-2 infection by detecting the virus's genetic material. In PCR testing, a machine located in a laboratory or at a point of care, depending on the test, runs a series of reactions. These reactions first convert the virus's ribonucleic acid (RNA), if present, into deoxyribonucleic acid (DNA) and then amplify it (make millions of copies of the DNA); the test then detects this DNA. By running multiple amplification cycles, a PCR test can sense even low levels of viral genetic material in a patient's sample, so these tests tend to be highly sensitive.

We have determined that requiring a maximum of 24 amplification cycles for PCR tests to qualify a diagnosis of COVID-19 is not justified because such a requirement, in and of itself, is arbitrary and would not ensure testing validity. While generally the fewer number of amplification cycles on a sample that shows a positive indicates a higher viral load, the number of amplification cycles used to detect genetic material is not necessarily the same across different PCR tests – meaning that the same sample tested on multiple PCR tests may take different numbers of amplification cycles to get the same result. Accordingly, different amplification cycle cut-offs may be justified for different PCR tests. The variability across tests is one reason why Petitioner's request would not be justified.

Another reason why Petitioner's request is not justified is that the number of amplification cycles used is just one factor that affects the reliability of a PCR result. Other factors that help ensure reliable testing include: sufficiently sensitive analytical Limit of Detection; robust performance when there are interfering substances in the sample; and good sensitivity when testing known positive and known negative clinical samples. Rather than impose an across-the-board amplification cycle cutoff, we believe that the better approach is the one taken in FDA's June 2020 Guidance, which explains sponsors' obligation to ensure reliable testing.[26] Not only does the June 2020 Guidance emphasize sponsors' responsibility for using reliable testing, but FDA's review of INDs also helps ensure that investigations are designed in ways that allow meaningful scientific inferences to be drawn. Indeed, FDA reviews reports regarding the validation of SARS-CoV-2 testing that sponsors include in their IND submissions.

[24] As support for the 24-amplification-cycle cutoff, Petitioner refers to a study that "the CDC relied upon [which] reports finding no 'live' virus in any samples whose cycle threshold is greater than 24" as well as a study "by a team at Oxford." CP at 8. However, the studies cited by Petitioner do not in fact conclude that 24 amplification cycles is a necessary cutoff for ensuring the accuracy and validity of PCR tests in patients. Rather, the studies correlate cycle thresholds with positive in vitro cell cultures.
[25] June 2020 Guidance at 17.
[26] See id.

Accordingly, we have determined that FDA's existing guidance and IND review process already provides adequate oversight with respect to testing. We do not believe that Petitioner's proposed cutoff of 24 amplification cycles is scientifically justified.

3. Interruption of Transmission be a Primary Endpoint

Petitioner asserts that "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." CP at 9. Specifically, Petitioner notes that "the clinical trials also do not call for interruption of transmission of the disease as a primary endpoint. . . ." CP at 9. Petitioner further asserts that "[t]he 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." CP at 9. Petitioner notes that:

> The Chief Medical Officer at Moderna, Tal Zaks, openly admitted that the "trial will not demonstrate prevention of transmission."[] 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."

CP at 9.

While FDA has not required that COVID-19 vaccine trials assess person-to-person transmission, authorization or licensure of safe vaccines is nevertheless justified when the vaccines have been shown to be effective at protecting vaccinated individuals from symptomatic COVID-19. Vaccines that reduce the incidence of disease will play an important role in mitigating the current public health emergency. Moreover, we do not interpret the applicable statutory standards for licensure or authorization as requiring that the primary objective of COVID-19 vaccine efficacy trials be a demonstration of reduction in person-to-person transmission. Effectiveness may be shown by a reduction in the incidence of disease in vaccinated individuals. We therefore disagree with Petitioner's suggestion that these vaccine trials must demonstrate interruption of transmission of the disease as a primary endpoint.

4. T-cell Reactivity and Response

Petitioner requests FDA to amend the Phase 3 trials of the COVID-19 Vaccines' study design to provide that "participants be tested for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination." CP at 2. In support of this request, Petitioner quotes an article in which the authors state that "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."[27,28] CP at 10.

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[27] Sette, A., Crotty, S. Pre-existing immunity to SARS-CoV-2: the knowns and unknowns, Nat Rev Immunol 20, 457–458 (2020) (Sette Article), https://doi.org/10.1038/s41577-020-0389-z.

[28] We note that, while Petitioner's request pertains to a Phase 3 trial, the language that Petitioner quotes from the Sette Article relates to Phase 1 trials:

> Pre-existing $CD4^+$ T cell memory could also influence vaccination outcomes, leading to a faster or better immune response, particularly the development of neutralizing antibodies, which generally depend on T cell help. At the same time, pre-existing T cell memory could also act as a confounding factor, especially in relatively small phase I vaccine trials. For example, if subjects with pre-existing reactivity were assorted unevenly in different vaccine dose groups, this might

The authors of the article cited by Petitioner state that "[i]t is frequently assumed that pre-existing T cell memory against SARS-CoV-2 might be either beneficial or irrelevant. However, there is also the possibility that pre-existing immunity might actually be detrimental."[29] FDA agrees that the implications of T-cell reactivity are not yet well-understood, and it is unclear at this time whether or how T-cell reactivity would impact the results of the clinical trial. Insofar as T-cell reactivity could be a confounding variable that could bias the comparison between the placebo and active vaccine groups, randomization would be an appropriate strategy to minimize any variability. Randomization ensures that the groups are balanced with regard to identified and unidentified confounders. FDA's IND reviewers consider the adequacy of sponsors' strategies to reduce bias, such as randomization, and FDA's June 2020 Guidance recommends randomization.[30] Therefore, to the extent that T-cell reactivity could be a confounding variable, we believe that there are adequate safeguards to protect against bias between the placebo and active vaccine groups. Additionally, we are not aware of any basis to conclude that any preexisting T-cell reactivity among study participants undercuts the comparability between the placebo and active vaccine groups.

Therefore, requiring testing for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination would not provide meaningful information for purposes of FDA's authorization or licensure of a vaccine to prevent COVID-19.[31]

For the foregoing reasons, FDA denies Petitioner's request that the vaccine trials conduct such testing.

C. The Petition for Stay of Action

In the PSA, Petitioner requests FDA to "[s]tay the Phase III trials of mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722) until the study designs are amended" to conform with Petitioner's request. PSA at 2. Specifically, Petitioner requests the study designs 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

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> lead to erroneous conclusions. Obviously, this could be avoided by considering pre-existing immunity as a variable to be considered in trial design. Thus, we recommend measuring pre-existing immunity in all COVID-19 vaccine phase I clinical trials.

Id. at 458.

[29] Id. at 458.

[30] See Id. at 12 ("Later phase trials, including efficacy trials, should be randomized, double-blinded, and placebo controlled").

[31] To the extent that Petitioner's request is based on the assumption that measuring T-cell reactivity pre and post vaccination would provide meaningful information regarding efficacy, Petitioner has not provided support for this proposition. We believe that a vaccine that has been shown to safely prevent symptomatic COVID-19 can satisfy the relevant statutory standards and play an important role in addressing COVID-19.

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

PSA at 2.

1. Criteria for Granting an Administrative Stay of Action

We do not agree that the requests in the PSA are appropriate for a petition submitted under 21 CFR § 10.35. Petitioner's PSA seeks blanket requirements for trials involving investigational COVID-19 vaccines based on Petitioner's apparent policy views, whereas section 10.35 is designed to allow interested persons to request that the Agency hold in abeyance an identified, particular decision. However, assuming arguendo that the PSA does meet the threshold requirements in section 10.35, we describe the substantive issues raised by the PSA in this section and below.

FDA's regulation at 21 CFR § 10.35(e) sets out the standard for review of a petition for stay of action as follows, in part:

> The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition…The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:
> (1) The petitioner will otherwise suffer irreparable injury.
>
> (2) The petitioner's case is not frivolous and is being pursued in good faith.
>
> (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
>
> (4) The delay resulting from the stay is not outweighted by public health or other public interests.[32]

This section also contains a provision for the discretionary implementation of a stay in any proceeding if it is in the public interest and in the interest of justice (21 CFR § 10.35(e)).

As stated in the regulation, the Commissioner shall grant a stay if all four of the criteria in 21 CFR § 10.35(e) apply. As explained below, we find that Petitioner has failed to demonstrate three of the four criteria in section 10.35(e). Consequently, we need not address Petitioner's assertion that the PSA is not frivolous and is being pursued in good faith. FDA also has the discretion to grant a stay if it is in the public interest and in the interest of justice to do so. We also decline to grant the PSA on the basis that Petitioner has not established that a stay would be in the public interest or the interest of justice.

a. Petitioner Has Not Demonstrated Irreparable Injury

Petitioner contends that a stay must be granted because Petitioner will suffer irreparable injury. PSA at 11. Specifically, Petitioner argues that "once the FDA licenses this COVID-19 vaccine, states are expected to make this product mandatory, and hence without the FDA assuring proper efficacy trials of the vaccine *now*, the Petitioner will not have the opportunity to object to

[32] See 21 CFR § 10.35(e).

receiving the vaccine based on deficient clinical trials *later*." PSA at 3.[33] Petitioner also states that "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." PSA at 3.

Petitioner's claim of injury is too remote. Petitioner asserts that Petitioner will be forced to receive an inadequately vetted vaccine due to State-level mandatory vaccination requirements. However, the PSA does not seek a stay of any FDA decision that will force any individuals to receive a vaccine. FDA does not mandate vaccination. Petitioner seeks a stay of the Phase 3 trials of "mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722)." However, Petitioner has not demonstrated that the continuation of these trials will cause States to issue requirements that will in turn cause Petitioner to be vaccinated against Petitioner's will. There are numerous regulatory steps between the conduct of clinical trials and the existence of a vaccine that is available to the public—much less before any State, or other governmental entity makes any potential decisions regarding mandatory vaccination.[34] The continuation of clinical trials, alone, will not cause the asserted harm.

Furthermore, Petitioner has not produced any evidence that any mandatory requirements related to vaccination will be "based on inaccurate beliefs." PSA at 3, 11. Thus, not only is Petitioner's assertion that continuing clinical trials will harm Petitioner by leading to vaccination requirements too attenuated, but Petitioner's assertion about the beliefs that may motivate any potential vaccination requirement is unsupported and therefore also too attenuated. Petitioner has not demonstrated that the continuation of clinical trials will cause the asserted harm regarding "inaccurate beliefs."

Thus, Petitioner has not demonstrated that the continuation of clinical trials under FDA IND will cause irreparable injury.

b. Petitioner Has Not Demonstrated Sound Public Policy Grounds Supporting the Stay

Petitioner asserts, but does not provide evidence to support the assertion, that "the request demonstrates sound public policy." PSA at 2.

We do not agree that Petitioner has demonstrated sound public policy grounds supporting a stay. Petitioner seeks a stay of the Phase 3 trials of "mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722)." The FD&C Act provides a specific mechanism, called a "clinical hold," for prohibiting sponsors of clinical

[33] Petitioner also states that Petitioner will suffer irreparable harm if FDA does not assure "proper safety trials." PSA at 11. However, Petitioner characterizes the PSA as relating to efficacy trials. See, e.g., PSA at 3 (stating that the clinical trials are "inadequate to assesses efficacy"). We therefore assume the reference to safety is an error. Petitioner has submitted other very similar petitions to the Agency asserting similar harm if FDA does not assure "proper safety trials," so we assume that Petitioner may have copied and pasted this language in error.

[34] Concerns about potential State vaccine requirements are better directed to the States. FDA does not mandate use of vaccines. However, to the extent that Petitioner has concerns about inadequately vetted vaccines, we note that FDA's science-based decision-making process is designed to assure that any vaccine that is authorized or licensed meets all relevant statutory requirements.

investigations from conducting the investigation (section 505(i)(3) of the FD&C Act; 21 U.S.C. § 355(i)(3)). FDA's implementing regulations in 21 CFR § 312.42 identify the circumstances that may justify a clinical hold. Although the mechanism by which FDA may "stay" a clinical trial is to issue a clinical hold, Petitioner has not identified any basis under 21 CFR § 312.42 or section 505(i)(3) of the FD&C Act for any clinical trial that would justify a clinical hold.

We conclude that a stay of a clinical trial is warranted only when a basis has been demonstrated for a clinical hold in accordance with 21 CFR 312.42 and section 505(i)(3) of the FD&C Act. Because Petitioner has not identified any such basis, we disagree that Petitioner has demonstrated sound public policy grounds supporting the requested stay. We note that if FDA becomes aware of circumstances justifying clinical holds, FDA will order clinical holds in accordance with 21 CFR § 312.42 and section 505(i)(3) of the FD&C Act.

c. Delay Would Be Outweighed by Public Health or Other Public Interests

Finally, Petitioner asserts that any delay caused by the requested stay is not outweighed by the public health or other public interests. In support of this argument, Petitioner states that:

> 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.

PSA at 11.

Petitioner has not demonstrated that delay would be not be outweighed by public health or other public interests. Any vaccine to prevent COVID-19 will only be authorized or licensed based on FDA's science-based decision-making process to assure our standards for safety and effectiveness are met.[35]

In addition, the extraordinary current public health situation further argues against any unnecessary delay in the timely development of a COVID-19 vaccine that meets all relevant regulatory requirements. This is especially true when Petitioner has not identified a single basis for FDA to stay (or place on hold) any Phase 3 trials of "mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722)." Nor has Petitioner demonstrated that the requested endpoints are necessary (see discussion above). Delaying clinical trials for the sole purpose of requiring endpoints that are not scientifically necessary would compromise the public health and public interest in vaccine development.

In short, the public health and public interest in adequate and well-controlled clinical trials for COVID-19 vaccines is strong. We conclude that staying clinical trials without justification would not be in the public health or public interest, and Petitioner has not set forth any justification under our regulations for staying the "mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722)" clinical

[35] For a vaccine licensed under BLA, those standards are described in section II.A. above and Appendix I. For a vaccine with an emergency use authorization, those standards are described in section II.B. above.

trials. The interests of public health would not be served if a stay interfered with the conduct of clinical trials without justification.

2. Neither the Public Interest nor the Interest of Justice Support Granting a Discretionary Stay of Action

Section 10.35 also provides that FDA may grant a stay of administrative action if the Agency believes it is in the public interest and in the interest of justice. As discussed above, we do not agree that a stay is in the public interest or the interest of justice at this time. It is in the public interest and the interest of justice to ensure that "mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722)" clinical trials for COVID-19 vaccines continue. Stays (or clinical holds) are only justified when there is a basis to do so under 21 CFR § 312.42 and section 505(i)(3) of the FD&C Act. It is not in the public interest or the interest of justice to stay clinical trials in response to petitions to the Agency that fail to demonstrate any justification under 21 CFR § 312.42 and section 505(i)(3) of the FD&C Act for a hold.

For the foregoing reasons, the PSA is denied.

IV. Conclusion

FDA has considered Petitioner's requests as they relate to the "study design for the Phase III trials of mRNA-1273 (NCT04470427), BNT162 (NCT04368728), AZD1222 (NCT04516746), and Ad26.COV2.S (NCT04505722)." For the reasons given in this letter, FDA denies the requests in the CP and also denies the requests in the PSA. Therefore, we deny the Petitions in their entirety.

Sincerely,

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

cc: Dockets Management Staff

Appendix I: Aspects of Vaccine Development and Process for Licensure

A. Vaccines are Biologics and Drugs

Vaccines are both biological products under the Public Health Service Act (PHS Act) (42 U.S.C. § 262) and drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 321). The PHS Act defines a "biological product" as including a "vaccine…or analogous product…applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1). The FD&C Act defines drug to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man." 21 U.S.C. § 321(g)(1)(B).

Under the PHS Act, a biological product may not be introduced or delivered for introduction into interstate commerce unless a biologics license is in effect for the product. 42 U.S.C. § 262(a)(1)(A).

B. Clinical Investigations of Vaccines

Before a vaccine is licensed (approved) by FDA and can be used by the public, FDA requires that it undergo a rigorous and extensive development program that includes laboratory research, animal studies, and human clinical studies to determine the vaccine's safety and effectiveness. The PHS Act and the FD&C Act provide FDA with the authority to promulgate regulations that provide a pathway for the study of unapproved new drugs and biologics. 42 U.S.C. § 262(a)(2)(A) and 21 U.S.C. § 355(i). The regulations on clinical investigations require the submission of an Investigational New Drug application (IND), which describes the protocol, and, among other things, assures the safety and rights of human subjects. These regulations are set out at 21 CFR Part 312. See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).

The regulations provide that, once an IND is in effect, the sponsor may conduct a clinical investigation of the product, with the investigation generally being divided into three phases. With respect to vaccines, Phase 1 studies typically enroll fewer than 100 participants and are designed to look for very common side effects and preliminary evidence of an immune response to the candidate vaccine. Phase 2 studies may include up to several hundred individuals and are designed to provide information regarding the incidence of common short-term side effects, such as redness and swelling at the injection site or fever, and to further describe the immune response to the investigational vaccine. If an investigational new vaccine progresses past Phase 1 and Phase 2 studies, it may progress to Phase 3 studies. For Phase 3 studies, the sample size is often determined by the number of subjects required to establish the effectiveness of the new vaccine, which may be in the thousands or tens of thousands of subjects. Phase 3 studies are usually of sufficient size to detect less common adverse events.

If product development is successful and the clinical data are supportive of the proposed indication, the completion of all three phases of clinical development can be followed by submission of a Biologics License Application (BLA) pursuant to the PHS Act (42 U.S.C. § 262(a)), as specified in 21 CFR § 601.2.

C. Biologics License Applications

A BLA must include data demonstrating that the product is safe, pure, and potent and that the facility in which the product is manufactured "meets standards designed to assure that the

biological product continues to be safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i). FDA does not consider an application to be filed until FDA determines that all pertinent information and data have been received. 21 CFR § 601.2. FDA's filing of an application indicates that the application is complete and ready for review but is not an approval of the application.

Under § 601.2(a), FDA may approve a manufacturer's application for a biologics license only after the manufacturer submits an application accompanied by, among other things, "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency." The BLA must provide the multidisciplinary FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc.) with the Chemistry, Manufacturing, and Controls (CMC)[36] and clinical information necessary to make a benefit-risk assessment, and to determine whether "the establishment(s) and the product meet the applicable requirements established in [FDA's regulations]." 21 CFR § 601.4(a).

FDA generally conducts a pre-license inspection of the proposed manufacturing facility, during which production of the vaccine is examined in detail. 42 U.S.C. § 262(c). In addition, FDA carefully reviews information on the manufacturing process of new vaccines, including the results of testing performed on individual vaccine lots.

FDA scientists and physicians evaluate all the information contained in a BLA, including the safety and effectiveness data and the manufacturing information, to determine whether the application meets the statutory and regulatory requirements. FDA may also convene a meeting of its advisory committee to seek input from outside, independent, technical experts from various scientific and public health disciplines that provide input on scientific data and its public health significance.

As part of FDA's evaluation of a vaccine as a whole, FDA takes all the ingredients of a vaccine into account (including preservatives and adjuvants). FDA licenses a vaccine only after the Agency has determined that the vaccine is safe and effective for its intended use, in that its benefits outweigh its potential risks.

[36] Also referred to as Pharmaceutical Quality/CMC.