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-2225)

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 Dr. Sin Hang Lee (Petitioner) relating to the Phase 3 trial of the BNT162b vaccine to prevent the novel coronavirus SARS-CoV-2 (COVID-19):

- The citizen petition dated November 23, 2020 (the CP); and
- The petition for administrative stay of action dated November 25, 2020 (the PSA)

(collectively, the Petitions).

In the CP, Petitioner requests FDA to amend "the study design for the Phase III trial[] of BNT162b (NCT04368728)" to provide that:

> Before an EUA or unrestricted license is issued for the Pfizer vaccine, or for other vaccines for which PCR results are the primary evidence of infection, all "endpoints" or COVID-19 cases used to determine vaccine efficacy in the Phase 3 or 2/3 trials should have their infection status confirmed by Sanger sequencing, given the high cycle thresholds used in some trials. High cycle thresholds, or Ct values, in RT-qPCR test results have been widely acknowledged to lead to false positives.
>
> All RT-qPCR-positive test results used to categorize patient as "COVID-19 cases" and used to qualify the trial's endpoints should be verified by Sanger sequencing to confirm that the tested samples in fact contain a unique SARS-CoV-2 genomic RNA. Congruent with FDA requirements for a confirmed diagnosis of human papillomavirus (HPV) using PCR, the sequencing electropherogram must show a minimum of 100 contiguous bases matching the reference sequence with an Expected Value (E Value) $<10^{-30}$ for the specific SARS-CoV-2 gene sequence based on a BLAST search of the GenBank database (aka NCBI Nucleotide database).

CP at 1-2 (internal citation omitted).

In the PSA, Petitioner requests FDA to "[s]tay the Phase III trial of BNT162 (NCT04368728) until its study design is amended" to conform with Petitioner's request. PSA at 2. The Petitioner's request in the PSA is the same as that of the CP indicated above. PSA at 2.

This letter responds to the CP and the PSA in full. FDA has carefully reviewed 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.[1] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[2] 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. On November 20, 2020, Pfizer, Inc. (Pfizer) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine, BNT162b2, intended to prevent COVID-19.[3] As announced by FDA on December 11, 2020, the Agency is granting an EUA for the Pfizer-BioNTech COVID-19 Vaccine.[4]

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.[5,6] The Public Health Service Act (PHS Act) authorizes FDA to license biological products, including vaccines, if they have been demonstrated to be "safe, pure, and potent."[7] Based on the PHS Act and FDA's regulations, the licensure process for a vaccine requires the sponsor to establish, through carefully controlled

[1] 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.
[2] 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/.
[3] FDA Briefing Document, Pfizer-BioNTech COVID-19 Vaccine, Vaccines and Related Biological Products Advisory Committee Meeting, December 10, 2020 at 6, https://www.fda.gov/media/144245/download.
[4] EUA letter for Pfizer-BioNTech COVID-19 Vaccine dated December 11, 2020, https://www.fda.gov/media/144412/download.
[5] 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.
[6] Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[7] 42 U.S.C. § 262(a)(2)(C)(i)(I).

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.[8] 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."[9] 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 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.[10] 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)).[11]

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:

- 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.

[8] Vaccines, last updated June 2020, https://www.fda.gov/vaccines-blood-biologics/vaccines.
[9] 21 CFR § 601.2(d).
[10] 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[11] 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

- 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 *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.[12] 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.[13] 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.[14]

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 be reliable enough so that it is not likely to have happened by chance.[15] 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

[12] Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry, October 2020, https://www.fda.gov/media/142749/download.
[13] Id. at 3.
[14] Id. at 4.
[15] Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry, June 2020 (June 2020 Guidance), https://www.fda.gov/media/139638/download.

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 PDUFA goals letter and range from 6 – 10 months after the application has been filed.[16] 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 "the study design for the Phase III trial[] of BNT162b (NCT04368728)." FDA's investigational new drug process applies to the development of new drugs and biological products, including vaccines.[17]

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[18]) 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 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.[19] The IND describes the proposed clinical study in detail and, among other things, helps protect the safety and rights

[16] PDUFA Reauthorization Performance Goals And Procedures Fiscal Years 2018 Through 2022; https://www.fda.gov/media/99140/download.

[17] See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).

[18] 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.

[19] See 21 CFR § 312.20(a).

of human subjects.[20] 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),[21] 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 CFR § 312.22(a).

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.

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

[20] 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.

[21] 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.

order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or to suspend an ongoing investigation.[22]

B. The Citizen Petition

The Petitioner requests that FDA "amend" the clinical trial "study design" for the Phase 3 trial of "BNT162 (NCT04368728)," a product being developed by Pfizer, to include certain design characteristics. Because FDA does not itself create or amend drug or vaccine investigations,[23] we interpret the CP as asking that FDA require the sponsor to make the requested changes.[24] 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.

Turning to the specific requests, Petitioner asks that "[b]efore an EUA or unrestricted license is issued for the Pfizer vaccine, or for other vaccines" that use the polymerase chain reaction (PCR) testing as evidence of infection in clinical trials, the late-stage trials "should have their infection status confirmed by Sanger sequencing." CP at 1. The CP states that this is necessary "given the high cycle thresholds used in some trials" that "have been widely acknowledged to lead to false positives." CP at 1-2. The CP maintains that the Sanger sequencing should be used "to confirm that the tested samples in fact contain a unique SARS-CoV-2 genomic RNA." CP at 2.

1. Background Regarding Testing Technology and SARS-CoV-2 Testing

FDA agrees that accurate testing is an important part of ensuring the reliability of vaccine trial outcomes. An accurate test helps identify 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[25] and accurate for the purpose of confirming infection and should be validated before use."[26]

Nucleic acid-based amplification tests (NAAT), also referred to as 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

[22] 21 CFR § 312.42(a).
[23] Rather, sponsors are responsible for creating study designs. FDA reviews INDs and may place INDs on clinical holds pursuant to 21 CFR § 312.42 if the Agency identifies certain deficiencies.
[24] 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 clinical trials.
[25] Sensitivity and specificity are basic measures of performance for a diagnostic test. Together, they describe how well a test can determine whether a specific condition is present or absent. "Sensitivity" refers to how often the test is positive when the condition of interest is present; "specificity" refers to how often the test is negative when the condition of interest is absent. See Guidance for Industry and FDA Staff, Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests, March 2007, at 21 (Statistical Guidance for Diagnostic Tests), https://www.fda.gov/media/71147/download.
[26] June 2020 Guidance at 17.

levels of viral genetic material in a patient's sample, so these tests tend to be highly sensitive (especially laboratory PCR tests).

In a Sanger sequencing-based method, dideoxy-nucleotide (ddNTP) chain terminators are used to determine the specific nucleotide sequence of the target nucleic acid. Current Sanger sequencing-based methods are most commonly carried out via a multistep process, which includes not only appropriate sampling and nucleic acid extraction, but also: 1) conventional PCR amplification of the target region; 2) PCR cleanup for removal of unincorporated primers and nucleotides; 3) a sequencing reaction in which the PCR product is used as template for the incorporation of fluorescently labeled dideoxy chain terminators; 4) sequencing reaction cleanup for removal of unincorporated fluorescent dideoxy chain terminators; and 5) simultaneous size-dependent separation and nucleic acid sequence determination.

PCR, when used in conjunction with Sanger-based or other sequencing, can detect and identify viral genetic material in a clinical sample. Historically, PCR has been used with reverse transcription to amplify viral RNA to indicate whether there was a positive signal of any suitable genetic material present, and sequencing has been used to confirm the nucleic acid sequence of the amplified genetic material. As PCR technology has evolved, however, PCR testing does not need to be followed by Sanger or other sequencing for purposes of clinical diagnosis. Currently, reverse real-time PCR (RT-PCR) tests can both amplify and confirm the identity of viral genetic material in a single reaction, without a separate sequencing step.[27] Many of the NAATs for detection of SARS-CoV-2 that FDA has authorized are based on the technology that both amplifies and confirms viral genetic material without the need for an additional sequencing step.

We have determined there is not scientific merit in requiring the Phase 3 trial for BNT162 or other COVID-19 vaccine candidates to qualify a PCR diagnosis of COVID-19 with Sanger sequencing. Testing used to support the detection of SARS-CoV-2 infection should be sensitive and accurate, and PCR assays can be sufficiently sensitive and accurate without the need for Sanger sequencing.[28]

FDA's current recommendations for SARS-CoV-2 molecular diagnostic tests include that developers confirm the performance of their assay by testing a minimum of 30 positive specimens and 30 negative natural clinical specimens as determined by an authorized assay.[29] Additionally, the clinical performance data should demonstrate a minimum of 95% positive percent agreement (i.e., sensitivity) and negative percent agreement (i.e., specificity).[30] But FDA

[27] For more background on this topic, see A Closer Look at Coronavirus Disease 2019 (COVID-19) Diagnostic Testing, November 2020, https://www.fda.gov/media/143737/download.

[28] FDA has provided information and recommendations regarding validation testing for SARS-CoV-2 tests which reflect FDA's current thinking on the data and information that developers should submit to facilitate FDA's review of an EUA request for a SARS-CoV-2 test pursuant to Section 564 of the FD&C Act. See Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised), Immediately in Effect Guidance for Clinical Laboratories, Commercial Manufacturers, and Food and Drug Administration Staff, May 2020, at 17-20 (COVID-19 Testing Guidance), https://www.fda.gov/media/135659/download. These recommendations are based on the totality of scientific evidence currently available to FDA regarding the clinical performance estimates for molecular diagnostic tests (i.e., tests that detect SARS-CoV-2 nucleic acids from human specimens) that, under the current circumstances of the COVID-19 public health emergency, are generally necessary to satisfy the effectiveness and risk/benefit standards for issuance of an EUA.

[29] Id. at 18.

[30] Molecular Diagnostic Template for Commercial Manufacturers, July 2020, at 16 (Molecular Test Template), https://www.fda.gov/media/135900/download.

has not identified any need to require PCR testing for clinical cases to be followed by Sanger-based or other sequencing. We believe that clinical diagnoses can be supported following PCR analyses with a positive percent agreement and negative percent agreement greater than or equal to 95%.[31]

2. Petitioner's Argument Regarding HPV Testing

Petitioner asserts that Sanger sequencing confirmation would be "[c]ongruent with FDA requirements for a confirmed diagnosis of human papillomavirus (HPV) using PCR." CP at 2. As support, Petitioner refers to an FDA guidance document that recommends that, in some situations, PCR testing be followed by Sanger sequencing for the evaluation of a device's ability to detect HPV.[32] But the recommendations in that guidance have no applicability to the clinical trials for COVID-19 vaccines. The recommendations in the HPV Testing Guidance are for developers of new tests and relate to evaluation of new testing products. Specifically, the guidance recommends that developers of a new HPV test evaluate the ability of the new test to detect the targeted HPV genotypes by comparing the results obtained using the new test to results obtained using either an FDA-approved HPV test that detects the same genotypes, or PCR followed by Sanger sequencing.[33] That is, when developing a new HPV testing technology, one option for manufacturers to evaluate the accuracy of the technology is to confirm whether clinical specimens in fact contain the targeted HPV genotype by comparing the results from the manufacturer's test to the results from Sanger sequencing. The HPV Testing Guidance that Petitioner identifies does not recommend that PCR tests used to diagnose HPV infections in individuals be followed by Sanger sequencing when the tests are used for aiding the diagnosis of an individual's infection.

Therefore, we do not agree that Petitioner's example supports Petitioner's requested action.

3. Petitioner's Arguments Regarding Vaccine Trial Protocols

Petitioner asserts that a portion of the Pfizer public protocol[34] states that when study participants experience certain symptoms, they are to be tested with nasal swabs which will be tested for SARS-CoV-2. CP at 3-4. Petitioner points to three specific tests that are identified in the public protocol that have been issued EUAs by FDA: Cepheid Xpert Xpress SARS-CoV-2,[35] Roche

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[31] When a new test is evaluated by comparison to a non-reference standard because no consensus reference standard exists, information on the accuracy of the new test cannot be estimated directly. As a result, performance is demonstrated by the ability of the new test to agree sufficiently with a comparative method. The comparative results are called "positive percent agreement" (which corresponds to sensitivity) and "negative percent agreement" (which corresponds to specificity). The use of this language reflects that the estimates are not of accuracy but of agreement of the new test with the non-reference standard. See Statistical Guidance for Diagnostic Tests, at 11.

[32] Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection or Detection and Differentiation of Human Papillomaviruses, Guidance for Industry and Food and Drug Administration Staff, September 2017, (HPV Testing Guidance) https://www.fda.gov/media/92930/download.

[33] Id. at 17.

[34] Petitioner does not appear to identify the source of information about the Pfizer public protocol, but we note that Pfizer publicly released a protocol for the COVID-19 vaccine clinical trial. For purposes of this response, we presume that is the protocol that Petitioner refers to. See https://pfe-pfizercom-d8-prod.s3.amazonaws.com/2020-11/C4591001_Clinical_Protocol_Nov2020.pdf.

[35] See EUA letter for Xpert Xpress SARS-CoV-2 test dated March 20, 2020 (Xpert Xpress EUA Letter), https://www.fda.gov/media/136316/download.

cobas SARS-CoV-2 real-time RT-PCR test,[36] and Abbott Molecular/RealTime SARS-CoV-2 assay.[37] CP at 4. Petitioner states that these test kits "are very unreliable tools when they are used to determine whether the nasal swab sample collected from a symptomatic participant contains SARS-CoV-2 or not."[38] CP at 4. Petitioner states that this is because the results from these tests "cannot be analyzed by automated Sanger sequencing as the products of conventional PCR can" and that Sanger sequencing "is needed" for accuracy. CP at 4. As support for this assertion, Petitioner includes 11 points, listed in paragraphs (a)-(k). CP at 4-8. We respond to each of the Petitioner's listed points, using the same (a)-(k) paragraph designations. For clarity, we quote Petitioner's assertions and respond to each assertion:

a. Petitioner's assertion: "Nowadays DNA sequencing of the PCR amplicon of the genomic nucleic acid of the pathogen is a universally accepted technology for detection and for confirmation of infectious agents[.]" CP at 4.

   FDA response: We generally agree that "DNA sequencing" after PCR testing is "accepted technology," but we do not agree that this means PCR testing for SARS-CoV-2 must be followed by Sanger-based sequencing for confirmation of infectious agents. That is, for the reasons explained above, we do not agree that PCR testing for SARS-CoV-2 must be followed by Sanger-based sequencing in order to diagnose a clinical case of COVID-19,[39] in a clinical trial or otherwise.

b. Petitioner's assertion: "The World Health Organization (WHO) guidance . . . advised [real time PCR testing] with confirmation by nucleic acid sequencing when necessary." CP at 4. The guidance identified in this paragraph is "WHO Laboratory testing for coronavirus disease (COVID-19) in suspected human cases-Interim guidance dated 19 March 2020."[40] CP at 4.

   FDA response: This WHO guidance does not state that nucleic acid sequencing is critical in all circumstances in order to test accuracy. Rather, it states that the sequencing should be performed "when necessary." Among other things, the guidance contains testing recommendations for when the virus is known to be circulating in a geographic area, and for when the virus is not known to be circulating. When the virus is *not* known to be circulating in an area, the WHO guidance recommends sequencing as an option. But for areas with established COVID-19 virus circulation, the WHO guidance does not list

[36] See EUA letter for cobas SARS-CoV-2 dated October 15, 2020 (cobas EUA Letter), https://www.fda.gov/media/136046/download.
[37] See EUA letter for Abbott RealTime SARS-CoV-2 assay dated March 18, 2020 (Abbott EUA Letter), https://www.fda.gov/media/136255/download.
[38] We disagree with Petitioner's characterization. FDA has issued EUAs for the tests based on FDA's finding that the tests meet our regulatory standards for an EUA.
[39] This is the view of the U.S. Centers for Disease Control and Prevention (CDC) as well. The CDC case definition for COVID-19 notes that confirmatory laboratory evidence is "[d]etection of severe acute respiratory syndrome coronavirus 2 ribonucleic acid (SARS-CoV-2 RNA) in a clinical specimen using a molecular amplification detection test." The CDC does not include a specific recommendation for the use of sequencing as confirmatory evidence of SARS-CoV-2 infection. See CDC, Coronavirus Disease 2019 (COVID-19) 2020 Interim Case Definition, Approved April 5, 2020, https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/.
[40] WHO, Laboratory testing for coronavirus disease (COVID-19) in suspected human cases, Interim guidance, March 2020, https://www.who.int/publications/i/item/10665-331501.

sequencing as a recommended testing option. We note that this WHO guidance was drafted towards the beginning of the current pandemic, before the development of many of the NAATs that are currently in use. We also note that it does not make any recommendations related to confirming COVID-19 cases in vaccine clinical trials.

c. Petitioner's assertion: "The FDA also recognizes the inherent inaccuracy of the RT-qPCR[41] tests." CP at 5. As support for this statement, Petitioner identifies a letter of EUA that FDA issued the CDC for a specific test kit developed by the CDC.[42]

FDA response: We disagree. The letter of authorization did not make any statements regarding the general soundness of any particular type of testing technologies. Nothing in the letter suggests that samples that are positive for SARS-CoV-2 based on PCR testing should be confirmed by Sanger-based sequencing.

d. Petitioner's assertion: "In addition to false-negative results, these RT-qPCR test kits under EUA also generate false-positive test results." CP at 5.

FDA response: While we agree that no test is 100 percent accurate, this does not support Petitioner's request that FDA require PCR positive cases to be confirmed with Sanger-based sequencing in clinical trials for COVID-19 vaccines.

e. Petitioner's assertion: "The FDA has officially alerted clinical laboratory staff and health care providers of an increased risk of false-positive results with some of these commercial test kits permitted to be used under EUA." CP at 5.

FDA response: While FDA has identified some flaws with some tests, there are many FDA-authorized tests for which FDA has not issued any such alerts (including many tests that use PCR technology, such as Cepheid Xpert Xpress SARS-CoV-2, Roche cobas SARS-CoV-2 real-time RT-PCR test, and Abbott Molecular/RealTime SARS-CoV-2 assay). Moreover, FDA has not stated that samples identified as positive in PCR testing need to be confirmed by Sanger-based sequencing.

f. Petitioner's assertion: "To resolve the problems caused by these inherently inaccurate tests, the FDA's position is that false results can be investigated using an additional EUA RT-qPCR assay, and/or Sanger sequencing." CP at 5. As support for this statement, Petitioner cites the Molecular Test Template.[43]

FDA response: FDA's COVID-19 Testing Guidance states that all clinical tests should be validated prior to use, and provides recommendations for developers regarding testing

[41] Throughout the Petition, Petitioner asserts that the three assays identified in the Pfizer public protocol – Cepheid Xpert Xpress SARS-CoV-2, Roche cobas SARS-CoV-2 real-time RT-PCR test, and Abbott Molecular/RealTime SARS-CoV-2 assay – are "RT-qPCR" tests (i.e., NAATs that employ reverse transcription quantitative PCR). CP at 3-4. That assertion is incorrect. As stated in the EUAs for each of those tests, the three assays identified in the Pfizer public protocol are not quantitative tests; rather, each is only indicated for use in the *qualitative* detection of nucleic acid from SARS-CoV-2. See cobas EUA Letter, at 1; Xpert Xpress EUA Letter at 1; Abbott EUA Letter at 1.

[42] EUA letter for CDC 2019-Novel Coronavirus (2019-nCoV, renamed as SARS-CoV-2) Real-Time Reverse Transcriptase (RT)-PCR Diagnostic Panel dated March 15, 2020.

[43] See Molecular Test Template at 16.

that should be performed to demonstrate, in support of an EUA submission, that a SARS-CoV-2 test is validated based upon the underlying technological principles of the test.[44] However, FDA does *not* recommend that clinical results generated from PCR testing should be corroborated with Sanger-based sequencing in order to confirm the clinical performance of a test. Rather, the Molecular Test Template merely states that false results observed during the evaluation of an assay "*can* be investigated using an additional EUA RT-PCR assay, and/or Sanger sequencing" in order to provide the results of the discordant analysis to FDA.[45]

g. Petitioner's assertion: "According to the FDA guidance on molecular diagnosis of viral infection caused by human papillomavirus (HPV), a conventional PCR detection of genomic DNA followed by Sanger sequencing" is recommended. CP at 6.

   FDA response: See above discussion regarding the HPV Testing Guidance. FDA's recommendations regarding validation are for the testing technology, not clinical results. Petitioner's requested action would *not* be consistent with FDA's recommendations for clinical testing for HPV when performed by sensitive and accurate PCR tests.

h. Petitioner's assertion: "DNA sequencing verification is necessary for confirmation of the presumptive SARS-CoV-2-positive cases in the Pfizer vaccine's Phase II/III clinical trial" because the publicly available protocol states that the samples may be sent to a central laboratory using a Cepheid test that uses a "mean Ct value . . . as high as 42.9. . . . At Ct values between 36.0 and 44.9, many RT-qPCR positive test results are false positives." CP at 6.

   FDA response: While a test sample that is analyzed with a Ct value of 42.9 may find a very small concentration of viral fragments that may be of uncertain clinical significance, Petitioner does not provide any evidence that the Cepheid test being used in Pfizer's (or any other) clinical trial is being used to analyze samples that actually have a Ct value of 42.9. It appears that Petitioner found the 42.9 number in the Instructions for Use document for the Cepheid test, available on FDA's website.[46] However, the levels cited by Petitioner refer only to the range of concentrations analyzed to establish the test's limit of detection—not to the number of amplification cycles to be used for clinical diagnosis. Therefore, the levels cited by Petitioner do not demonstrate any accuracy problems with the test. The levels cited by Petitioner also do not demonstrate the need for follow-up Sanger-based sequencing.

i. Petitioner's assertion: "The results of the 3 RT-qPCR test kits used in the trial protocol are not comparable. A sample identified as negative by the Abbott kit can be classified as positive by the Cepheid kit." CP at 6.[47]

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[44] See COVID-19 Testing Guidance at 15, 18.
[45] Molecular Test Template at 16 (emphasis added).
[46] Xpert Xpress SARS-CoV-2, Instructions for Use, Table 4, https://www.fda.gov/media/136314/download.
[47] In this paragraph, Petitioner also includes a table from a study showing that the Cepheid Xpert kits have classified many Abbott kit negative cases as positives. See Basu, et al., Performance of Abbott ID NOW COVID-19 rapid nucleic acid amplification test in nasopharyngeal swabs transported in viral media and dry nasal swabs, in a New York City academic institution, Journal of Clinical Microbiology, May 2020,

FDA response: We agree that no test is 100 percent accurate, and there may be small differences in the analytical performance between different test kits – even kits that are well-validated and reliable. But we do not agree that this justifies Petitioner's requested action – requiring follow-up with Sanger-based sequencing. Tests that are well-validated and reliable may appropriately be used to confirm COVID-19 diagnoses in patients, including study participants.

j. Petitioner's assertion: "One of the Cepheid Xpert kit users has put out an alert" relating to false positives.[48] CP at 8.

FDA response: The alert Petitioner identifies was issued by Diagnostic Laboratory Services Inc., a clinical testing laboratory in Hawaii, and appears to concern the Cepheid GeneXpert testing platform,[49] not the Cepheid Xpert Xpress SARS-CoV-2 assay that is identified in the Pfizer public protocol and with which Petitioner takes issue. In any case, the fact that tests run by one laboratory in Hawaii on Cepheid GeneXpert instruments may have yielded suspect results does not justify the action requested by Petitioner. If sponsors for vaccine clinical trials are using SARS-CoV-2 tests that are well-validated and reliable, there is no scientific reason to require follow-up Sanger-based sequencing.

k. Petitioner's assertion: "Another group of users also found that some tested samples classified as positives by the Cepheid test kits cannot be confirmed with other test kits." CP at 8. The Petitioner cites to a study published in The Lancet Global Health for its proposition.[50]

FDA response: While the study cited by Petitioner found that some samples that were reported as positives using the Cepheid Xpert Xpress SARS-CoV-2 test did not report as positives using the comparison test, the study authors state that "[i]t is difficult to address the question on whether these specimens are true negative samples or low-positive samples with residual viral particles."[51] That is, for the samples that were positive using

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https://jcm.asm.org/content/58/8/e01136-20. But the Abbott test used in the study, which is compared to the Cepheid Xpert Xpress SARS-CoV-2 test, is the Abbott ID NOW COVID-19, not the Abbott RealTime SARS-CoV-2 assay that is listed in the public protocol identified by Petitioner. We note that, on May 14, 2020, FDA issued a release alerting the public to early data that suggest potential inaccurate results from using the Abbott ID NOW point-of-care test to diagnose COVID-19 because the test may return false negative results. See Coronavirus (COVID-19) Update: FDA Informs Public About Possible Accuracy Concerns with Abbott ID NOW Point-of-Care Test, May 14, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-informs-public-about-possible-accuracy-concerns-abbott-id-now-point. Therefore, the fact that the Abbott ID NOW COVID-19 and the Cepheid Xpert Xpress SARS-CoV-2 test produced different results is not surprising. The existence of different results from the Abbott ID NOW COVID-19 and the Cepheid Xpert Xpress SARS-CoV-2 test do not support a need for follow-up Sanger-based sequencing from PCR tests that have demonstrated a positive percent agreement and negative percent agreement greater than or equal to 95%, which include the tests identified in the Pfizer public protocol.

[48] See Diagnostic Laboratory Services Inc., Technical Alert, Possible False Positive SARS-CoV-2 (COVID-19) PCR, June 2020 (Technical Alert), https://dlslab.com/documents/bulletins/2020/tech-memo-sars-cov-2-pcr-possible-false-positive-6-19-2020.pdf.

[49] See Technical Alert subject header which refers to "Cepheid GeneXpert and BD Max Instruments may be Reporting False Positives."

[50] See Rakotosamimanana et al., GeneXpert for the diagnosis of COVID-19 in LMICs, The Lancet Global Health, October 2020, https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30428-9/fulltext.

[51] Id. at 1.

> Cepheid Xpert Xpress SARS-CoV-2 but not the other test, the study authors do not state that the samples were actually negative. Moreover, the study does not make any recommendations regarding the purported need to use follow-up Sanger-based sequencing on results that report to be positive using PCR testing.

In addition, Petitioner seems to also claim that follow-up Sanger sequencing is needed to address an asserted bias in the study design. Petitioner asserts that "it is commonly known" that injection of saline (i.e., the placebo) "will not cause fever, local redness and swelling, and severe pain, or systemic reactions." CP at 8. Study participants who receive a placebo therefore "intuitively and reasonably know that they were not injected with a vaccine[.]" CP at 9. Petitioner states that this is relevant to his requested action because, according to Petitioner, this makes placebo participants more likely to report symptoms than vaccine recipients, thereby leading to the use of test kits that will cause "[a] higher number of false-positive test results" among participants in the placebo arm. CP at 9. However, Petitioner has not pointed to any evidence that use of saline injections biases the reporting of symptoms – much less that this asserted compromise leads to a greater number of false positives. Therefore, we do not agree that Petitioner has demonstrated that purported unblinding justifies the action requested.[52,53,54]

C. The Petition for Stay of Action

In the PSA, Petitioner requests FDA to "[s]tay the Phase III trial of BNT162 (NCT04368728) until its study design is amended" to conform with Petitioner's request. PSA at 2. Specifically, Petitioner requests the study designs be amended to provide that:

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[52] Petitioner also states that he is willing to personally perform follow-up Sanger sequencing and that therefore "there is no excuse for the Sponsor" to not use such sequencing to confirm positive cases. CP at 9. We note that FDA has not stood in the way of Petitioner offering his services to Pfizer or any other sponsor.

[53] We note that one of the reasons Petitioner identifies for the requested action is that "both governments and employers may make this product mandatory (in general, or for airline or international travel) or may recommend it for widespread use." Id. at 2. Petitioner states that "proper efficacy trials" are needed because otherwise "the Petitioner and the public may not have the opportunity to object to receiving the vaccine." Id. Concerns about vaccination requirements or recommendations are better addressed to any government or private entity (e.g., airline) that may issue requirements or recommendations related to vaccination. FDA does not mandate use of vaccines. But to the extent that Petitioner's concern about vaccination requirements is based on questions about the magnitude of data supporting the vaccine's authorization, we note that our science-based review process for COVID-19 vaccines is designed to ensure that all statutory standards are satisfied prior to authorization or licensure.

[54] Petitioner also states that good efficacy data is needed because otherwise "any potential acceptance or mandate of these vaccines is likely to be based on inaccurate evidence regarding the vaccine." Id. Petitioner specifies that, by "inaccurate evidence," Petitioner means "that it will stop transmission of the virus from the vaccine recipient to others and/or that it will reduce severe COVID-19 disease and deaths." Id. Petitioner states that "[t]he Pfizer trial protocol is currently not designed to determine whether either of those objectives can be met." Id. at 2-3. To the extent that Petitioner is asserting that lack of Sanger follow-up testing means that any FDA authorization or license will be "based on inaccurate evidence," we disagree. As we explain in this response, lack of Sanger-based follow-up testing does not itself call into question the accuracy of the testing used in vaccine clinical trials. FDA has provided guidance emphasizing the need for accurate and reliable testing, and FDA has reviewed trial protocols with this need in mind. But Petitioner seems to also assert that there is something "inaccurate" in the fact that the Pfizer public protocol that Petitioner identifies does not include endpoints of preventing severe COVID-19 or stopping transmission. As FDA explains in its response to the citizen petition submitted under Docket Number FDA-2020-P-2180, FDA does not agree that those are necessary endpoints to support authorization. See Appendix A. Moreover, we do not agree that there is anything "inaccurate" about these endpoints not being used in any particular clinical trial.

> Before an EUA or unrestricted license is issued for the Pfizer vaccine, or for other vaccines for which PCR results are the primary evidence of infection, all "endpoints" or COVID-19 cases used to determine vaccine efficacy in the Phase 3 or 2/3 trials should have their infection status confirmed by Sanger sequencing, given the high cycle thresholds used in some trials. High cycle thresholds, or Ct values, in RT-qPCR test results have been widely acknowledged to lead to false positives.
>
> All RT-qPCR-positive test results used to categorize patient as "COVID-19 cases" and used to qualify the trial's endpoints should be verified by Sanger sequencing to confirm that the tested samples in fact contain a unique SARS-CoV-2 genomic RNA. Congruent with FDA requirements for a confirmed diagnosis of human papillomavirus (HPV) using PCR, the sequencing electropherogram must show a minimum of 100 contiguous bases matching the reference sequence with an Expected Value (E Value) $<10^{-30}$ for the specific SARS-CoV-2 gene sequence based on a BLAST search of the GenBank database (aka NCBI Nucleotide database).

PSA at 2 (internal citation omitted).

1. Criteria for Granting an Administrative Stay of Action

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.[55]

Section 10.35(e) 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 (§ 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

[55] 21 CFR § 10.35(e).

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. Petitioner's argument is that "once the FDA licenses this COVID-19 vaccine, states are expected to make this product mandatory, and 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*." PSA at 10 (emphasis in original). Petitioner also asserts that once FDA licenses the vaccine, "both governments and employers may make this product mandatory (in general, or for airline or international travel)" and that if the conditions are not satisfied "the vaccine will not have been properly tested." PSA at 2. Petitioner continues that "[i]f the vaccine is not properly tested, important public policy decisions regarding its use will be based on misleading evidence." PSA at 2-3.

Petitioner's claim of injury is too remote. Petitioner asserts that Petitioner will be forced to receive an inadequately vetted vaccine due to mandatory vaccination requirements that purportedly may be issued by entities such as airlines and States. However, the PSA does not seek a stay of any FDA decision that will force any individuals to receive vaccines. FDA does not mandate vaccination. Rather, Petitioner seeks to stay a Phase 3 clinical trial due to asserted problems with the testing protocol but has not demonstrated that the continuation of the trial will cause States, airlines, or any other entity 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 and distribution of a vaccine that is available to the public – much less before any State or other entity makes any potential decisions regarding mandatory vaccination.[56] The continuation of clinical trials, alone, will not cause the asserted harm.[57]

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 does not make any argument about sound public policy, but Petitioner does assert that the public interest weighs in favor of the requested relief "because improving the inaccurate determination of primary endpoints (i) will comport with the best scientific practices, (ii) increase public confidence in the efficacy of a product likely to be mandated or intended for widespread use, and (iii) not doing so will have the opposite result and create uncertainties regarding the efficacy of and need for the COVID-19 vaccines." PSA at 3.

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[56] 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 approved meets all relevant statutory requirements.

[57] Furthermore, for the reasons described above, we do not agree with Petitioner that it is problematic for clinical trials to use PCR testing of study participants. We also do not agree with Petitioner that the proposed solution—following PCR diagnoses with Sanger-based sequencing—is necessary. Therefore, we do not agree with Petitioner's assertion that there is harm to begin with.

We do not agree that Petitioner has demonstrated sound public policy grounds supporting a stay. Petitioner seeks a stay of a Phase 3 clinical trial. 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.

We also note that we disagree with the Petitioner's justification for the request that PCR clinical diagnoses of COVID-19 be followed with Sanger-based sequencing (see discussion above). It would not be sound public policy to require testing protocols that lack scientific merit. Requiring scientifically-unjustified protocols would add unnecessary costs to the clinical trial process, which could disincentivize important medical research.

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

Petitioner does not make any specific arguments that delay resulting from the stay would not be outweighed by public health or other public interests. However, Petitioner does assert that without granting the requested relief, acceptance of the vaccine "is likely to be based on inaccurate evidence regarding the vaccine, namely that it will stop transmission of the virus from the vaccine recipient to others and/or that it will reduce severe COVID-19 disease and deaths." PSA at 3. Petitioner further states that the "Pfizer trial protocol is currently not designed to determine whether either of those objectives can be met." PSA at 3.

We assume that Petitioner believes that delay resulting from the stay would not be outweighed by public health or other public interests because Petitioner believes that the requested stay would lead to more "accurate" evidence about the vaccine's effectiveness.

First and foremost, any vaccine to prevent COVID-19 will only be authorized or licensed based on FDA's science-based decision-making process to assure that the relevant regulatory requirements are met.

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 clinical trials under FDA IND.[58] Furthermore, Petitioner has not demonstrated that the requested relief will lead to more "accurate" effectiveness results, because Petitioner has not demonstrated that there is scientific merit in requiring that COVID-19 cases be confirmed using follow-up Sanger-based sequencing (see discussion above).

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

[58] See discussion above regarding Petitioner's failure to identify any basis for clinical holds under 21 CFR § 312.42 and section 505(i)(3) of the FD&C Act.

would not be in the public health or public interest, and Petitioner has not set forth any justification under our regulations for staying trials that are under FDA IND. 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

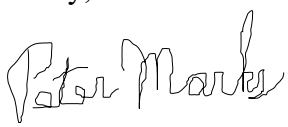
Section 10.35 also provides that FDA may grant a stay of administrative action if the Agency believes it is in the public interest and in the interest of justice. As discussed above, we do not agree that a stay is in the public interest or the interest of justice at this time. It is in the public interest and the interest of justice to ensure that clinical trials for COVID-19 vaccines continue to determine whether there are vaccines that meet all relevant regulatory requirements. Stays (or clinical holds) may only be 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 a Petition that fails to demonstrate any justification under 21 CFR § 312.42 and section 505(i)(3) of the FD&C Act for a hold.

Furthermore, if we required unnecessary steps in the testing to confirm COVID-19 diagnoses, the public interest would not be served because clinical trials should not be required to include protocols that lack scientific merit. Requiring scientifically-unjustified protocols would add unnecessary costs to the clinical trial process, which could disincentivize important medical research.

IV. Conclusion

FDA has considered Petitioner's requests as they relate to the "study design for the Phase III trial[] of BNT162b (NCT04368728)" and COVID-19 vaccine clinical trials. 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)[59] 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.

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