December 11, 2020

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

Re: Citizen Petitions and Petitions for Administrative Stay of Action (Docket Number FDA-2020-P-1601)

Dear Mr. Siri,

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

- The citizen petition dated June 17, 2020 (the CP);
- The petition for administrative stay of action dated June 17, 2020 (the PSA);
- The amended petition for administrative stay of action dated June 22, 2020 (the Amended PSA); and
- The amended citizen petition dated July 20, 2020 (Amended CP)

(collectively, the Petitions).[1]

In the CP, Petitioner requests that FDA

> a. Require all Phase II and III trials of vaccines against COVID-19 include a placebo control group (i.e., a placebo comparator group).
>
> b. The placebo shall be a saline injection without anything added. If the vaccine and saline are visually distinguishable, opaque vials should be used.
>
> c. The placebo control group shall be of at least equivalent size to the experimental group.
>
> d. All systemic adverse reactions, adverse events, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue arising or exacerbated post-vaccination shall be documented for each subject post-vaccination for a period of at least twelve months for adults, thirty-six months for children and teenagers, and sixty months for infants and toddlers.

CP at 1.

[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-1768, FDA-2020-P-1769, FDA-2020-P-1770, FDA-2020-P-2096, and FDA-2020-P-2180. FDA is responding separately to those petitions.

In the Amended CP, Petitioner requests that FDA, for Phase 2 and Phase 3 trials of COVID-19 vaccines,

> require any and all adverse events and reactions (including, but not limited to, systemic adverse reactions, adverse events, non-serious adverse event [sic], serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue of any degree or type arising or exacerbated post-vaccination, whether suspected, unexpected, expected or otherwise, and whether or not considered related to the vaccine) be documented for the entire duration of the clinical trial

(Amended CP at 1) and that "all adverse events and reactions for each subject be tracked post-vaccination for a minimum period of twelve months for adults, thirty-six months for children, and sixty months for infants and toddlers" (Amended CP at 2). Petitioner also requests that FDA amend the FDA guidance document entitled Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry (the June 2020 Guidance)[2] to provide, for Phase 3 studies of COVID-19 vaccines, "more specific and appropriate guidance on the number of subjects receiving the vaccine and placebo…and…require at least 20,000 subjects receive the COVID-19 vaccine with a 1:1 randomization between vaccine and placebo groups." Amended CP at 2. Petitioner further requests that FDA "formally adopt [the June 2020 Guidance], with the necessary flexibility, as formal regulatory requirements." Amended CP at 2.

In the PSA, Petitioner requests that FDA

> stay…the approval of the application for any Phase II and III trials of vaccines against COVID-19, including for ChAdOx1 nCoV-19, that do not include a placebo control group (i.e., a placebo comparator group) until:
>
> a. the study design for the trial is amended to include a placebo control group (i.e., a placebo comparator group);
>
> b. the placebo is specified as a saline injection and, if visually distinguishable from the vaccine, both should be packaged in opaque vials; and
>
> c. the placebo control group is of at least equivalent size to the experimental group.

PSA at 1.

In the Amended PSA, Petitioner repeats the requests in the PSA and further asks that FDA require such studies to document

> all systemic adverse reactions, adverse events, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue arising or exacerbated post-vaccination…for each subject post-vaccination for a period of at least twelve months for adults, thirty-six months for children and teenagers, and sixty months for infants and toddlers.

Amended PSA at 1.

This letter responds to the CP, the Amended CP, the PSA, and the Amended PSA in full. We have 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

[2] Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry, June 2020, https://www.fda.gov/media/139638/download.

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.

Here is an outline of our response:

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.[3] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[4] 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 Are Safe

1. Vaccines Are Shown to Be Safe at the Time of Licensure

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." 42 U.S.C. § 262(a)(2)(C)(i)(I). Prior to approval by FDA, vaccines are extensively tested in non-clinical studies and in humans. FDA's regulations describe some of the extensive data and information that each sponsor of a vaccine must submit to FDA in order to demonstrate the product's safety before FDA will consider licensing the vaccine. FDA requires that the sponsor's application include, among other things, data derived from nonclinical and clinical studies showing the product's safety, purity, and potency; a full description of manufacturing methods for the product; data establishing the product's stability through the dating period; and a representative sample of the product and summaries of results of tests performed on the lot(s) represented by the sample. 21 CFR § 601.2(a).

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] Only when FDA's standards are met is a vaccine licensed.

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" (emphasis added). 21 CFR § 601.2(d). Therefore, the manufacturers of vaccines that have been licensed in the United States (U.S.) have necessarily demonstrated the safety of the vaccines

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[3] 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.
[4] 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/.
[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] Vaccines, last updated June 2020, https://www.fda.gov/vaccines-blood-biologics/vaccines.

within the meaning of the applicable statutory and regulatory provisions before the vaccines were licensed and allowed to be marketed.

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

2. Vaccine Safety Continues to Be Monitored Post-Licensure

FDA's oversight of vaccine safety continues after licensure of the product. Once the licensed vaccine is on the market, post-marketing surveillance of vaccine safety is conducted in order to detect any rare, serious, or unexpected adverse events, as well as to monitor vaccine lots. FDA employs multiple surveillance systems and databases to continue to evaluate the safety of these vaccines. In certain cases, the FDA may require the manufacturer to conduct post-marketing studies to further assess known or potential serious risks.

For more information on post-licensure safety monitoring of vaccines, see Appendix II of this letter, *Aspects of Vaccine Postmarketing Safety Monitoring*.

B. An Emergency Use Authorization for a COVID-19 Preventative Vaccine Is Issued Only If the Relevant Statutory Standards Are Met

1. 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 U.S. citizens living abroad, and that involves the virus that causes COVID-19.[8] 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)).[9]

[8] 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[9] 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

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 (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.

2. Although EUAs are governed under a different statutory framework than Biologics License Applications (BLAs), FDA has made clear that issuance of an EUA for a COVID-19 vaccine would require that the vaccine demonstrate 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 provided recommendations that describe key information that would support issuance of an EUA for a vaccine to prevent COVID-19.[10] 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.[11] FDA 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.[12]

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

[10] Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry, October 2020, https://www.fda.gov/media/142749/download.
[11] Id at 3.
[12] Id at 4.

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.[13] 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.

3. 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.[14] 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.

- Importantly, FDA has made clear that any vaccine that meets FDA's standards for effectiveness is also expected to meet the Agency's safety standards. FDA has stated that the duration of safety follow-up for a vaccine authorized under an EUA may be shorter than with a BLA (which the Agency expects will ultimately be submitted by manufacturers of vaccines that are authorized under an EUA). Specifically, FDA's guidance to manufacturers recommends that data from Phase 3 studies to support an EUA include a median follow-up duration of at least 2 months after completion of the full vaccination regimen.[15] Furthermore, robust safety monitoring will be conducted after a vaccine is made available. This monitoring is also done for other newly-approved vaccines and will be expanded for the use of any COVID-19 vaccine. The monitoring systems include the Vaccine Adverse Event Reporting System (VAERS), the FDA's Biologics Effectiveness and Safety (BEST) System, and the CDC's Vaccine Safety Datalink. In addition, the FDA has a partnership with the Centers for Medicare & Medicaid Services (CMS) to study vaccine safety. Other tools to monitor vaccine safety are under development. Collectively, these programs will help detect any new, unusual and rare side effects after vaccination that might not have been observed during clinical trials, as well as monitor for increases in any known side effects.

4. 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

[13] Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry, June 2020, https://www.fda.gov/media/139638/download.
[14] PDUFA Reauthorization Performance Goals And Procedures Fiscal Years 2018 Through 2022; https://www.fda.gov/media/99140/download.
[15] October 2020 Guidance.

The Petitions all pertain to Phase 2 and 3 clinical studies of investigational vaccines to prevent COVID-19. FDA's investigational new drug process applies to the development 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 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 U.S. 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 IND 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

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[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.

[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; 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 web page, last updated November 2017, https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.

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 order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or to suspend an ongoing investigation.[21]

B. The Citizen Petitions

In the CP and the Amended CP, Petitioner requests that FDA amend late-phase clinical studies of COVID-19 vaccines to have certain design characteristics relating to the use of a placebo control group and the documentation of adverse events. CP at 1; Amended CP at 1-2. In the Amended CP, Petitioner also requests that FDA take certain actions relating to the June 2020 Guidance. Amended 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 safety and effectiveness of the investigational product.

[21] 21 CFR § 312.42(a).

[22] 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.

[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 clinical trials.

Below, we discuss the requested changes to study designs and actions relating to the guidance document.[24]

1. Petitioner's Requests for Changes to the Design of Certain Clinical Studies

In this section, we address Petitioner's requests regarding changes to the study designs in clinical studies of COVID-19 vaccines relating to the use of placebo control groups and the documentation of adverse events.[25]

As explained above, a sponsor must submit an IND to FDA before a clinical trial may be conducted. FDA's review of an IND includes a review of the plan or protocol which describes, among other things, the design of the clinical study, including the use of control groups and a description of the documentation of adverse events that may occur.

a. Placebo Control Groups

Petitioner requests that FDA "[r]equire all Phase II and III trials of vaccines against COVID-19 include a placebo control group (i.e., a placebo comparator group)," that "[t]he placebo…be a saline injection without anything added," that "[i]f the vaccine and saline are visually distinguishable, opaque vials…be used," and that '[t]he placebo control group…be of at least equivalent size to the experimental group." CP at 1.

Petitioner also asserts that

> most of the FDA-approved Phase II and III study designs for potential COVID-19 candidate vaccines appear to include a saline placebo control group…Unfortunately, this is not true for all of the COVID-19 vaccine trials approved by the FDA. For example, the Phase I/II clinical trial of the COVID-19 vaccine ChAdOx1 nCoV-19, currently under development by AstraZeneca, initially provided that the control group would receive a "Saline Placebo." After approving this study design, the FDA inexplicably approved changing the control from a "Placebo Control" to "MenACWY," which is another vaccine for a bacterial infection unrelated to COVID-19.

CP at 4; Amended CP at 9. Petitioner includes a link to study NCT04324606 on the ClinicalTrials.gov website.[26] CP at 4 footnote 13; Amended CP at 9 footnote 31.

i. Use of Placebo Control Groups

[24] Petitioner's principal arguments in support of the requested actions appear to hinge on a belief for the need for adequate and well-controlled clinical trials. As stated in the main text, we agree with Petitioner that robust, adequate, and well-controlled trials are essential. But we do not agree that Petitioner has identified a need for FDA to take the requested action. We note that one of the reasons the Petitioner identifies as supporting the proposal is that "states in the United States are expected to mandate the vaccine for all their residents." CP at 4; Amended CP at 2. 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.

[25] To the extent that Petitioner is requesting in the CP and Amended CP that INDs be put on clinical hold, we refer Petitioner to the discussion in section III.A. of this response.

[26] https://clinicaltrials.gov/ct2/history/NCT04324606.

We have determined that there are no grounds for FDA to require any changes to Phase 2 or Phase 3 clinical trials for COVID-19 vaccines that are under FDA IND to require that they use placebos for control groups, and Petitioner has not identified any such grounds.

The purpose of control groups is to allow discrimination of outcomes between subjects in the treatment group and those in the control group. While in many cases a placebo might be an appropriate control, other choices for control groups may sometimes be appropriate, and the choice of the control group should be considered in the context of standard therapies, the adequacy of the evidence to support the chosen design, and ethical considerations.[27] FDA agrees with Petitioner that the safety and effectiveness of COVID-19 vaccines must be supported by adequate and well-controlled clinical trials. In the context of investigational studies for COVID-19 vaccines, FDA has stated that later phase trials should be placebo controlled.[28] FDA has also stated in the June 2020 Guidance that, if availability of a COVID-19 vaccine proven to be safe and effective precludes ethical inclusion of a placebo control group, that vaccine could serve as the control treatment in a study designed to evaluate efficacy with noninferiority hypothesis testing.[29] We believe that FDA's existing guidance strikes an appropriate balance of recommending placebo controls, while also acknowledging that other types of controls may also be acceptable in some circumstances.

We also believe our oversight of clinical trials already allows the Agency to ensure that appropriate inferences can be drawn from late-stage trials. FDA has a robust process for reviewing INDs and ensuring that Phase 2 and Phase 3 clinical trials are designed in such a way as to allow appropriate inferences to be drawn. Indeed, FDA's regulations allow the Agency to place on clinical hold any Phase 2 or Phase 3 trials for which the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives. 21 CFR § 312.42(b)(2)(ii). Therefore, if FDA identifies problems with clinical trial design related to the use of control groups, FDA may address such problems.

In addition, the only example of a clinical trial that Petitioner has identified as not involving a placebo control is a study of ChAdOx1n CoV-19 that uses MenACWY instead of a placebo. However, we note that the study that Petitioner refers to – NCT04324606 – is listed on ClinicalTrials.gov as being conducted "in U K healthy adult volunteers" in locations in the United Kingdom, and as not studying a U.S. FDA-regulated drug product.[30] Because the study appears to be a study that is being conducted outside the U.S. and has not been submitted to FDA as part of an IND, FDA does not have an oversight role for this study.

In sum, Petitioner has not identified a basis for FDA to impose any requirements related to Phase 2 or Phase 3 trials using placebo comparators. We therefore deny Petitioner's request.[31]

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[27] See, e.g., E10 Choice of Control Group and Related Issues in Clinical Trials; Guidance for Industry, May 2001, https://www.fda.gov/media/71349/download.

[28] June 2020 Guidance.

[29] Id. at 12.

[30] A Phase I/II Study to Determine Efficacy, Safety and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in UK Healthy Adult Volunteers, at ! https://clinicaltrials.gov/ct2/show/NCT04324606?term=NCT04324606&draw=2&rank=1.

[31] To the extent that Petitioner's request regarding the use of placebos could be interpreted as a request for FDA to issue a prospective rule that would bind all sponsors of any future Phase 2 or Phase 3 trials for COVID-19 vaccines, we also deny that request. There may be multiple ways to design adequate and well-controlled clinical trials, and a

ii. Saline Placebo Control Groups

Petitioner also requests that FDA require that the placebo be a saline injection without anything added. We have determined that there are no grounds to require any changes to Phase 2 or Phase 3 clinical trials for COVID-19 vaccines that are under FDA IND to require that they use saline injections for placebos, and Petitioner has not identified any grounds. Saline injection placebos may be used by sponsors to blind study subjects and investigators as to who is receiving the control and who is receiving the investigational product, but other types of placebos may also be used in ways that ensure blinding. FDA has already taken many steps to provide recommendations to sponsors of COVID-19 vaccines regarding the design of adequate and well-controlled COVID-19 vaccine trials, including issuance of two guidance documents regarding COVID-19 vaccine development and thorough reviews of INDs submitted to the Agency related to COVID-19 vaccine trials. We believe that FDA's existing guidance, in combination with FDA's oversight of clinical trials, strikes an appropriate balance of ensuring adequate and well-controlled trials, while not imposing requirements that would preclude study designs that may be justified.

In addition, the only example of a clinical trial that Petitioner has identified as not using a saline injection placebo control is a study for ChAdOx1n CoV-19 that uses MenACWY as a control. However, as stated above, we note that the study that Petitioner refers to – NCT04324606[32] – is not one for which FDA has an oversight role.

In sum, Petitioner has not identified a basis for FDA to impose any requirements related to Phase 2 or Phase 3 trials using saline injection for placebos. We therefore deny Petitioner's request.[33]

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regulation that would limit trial designs to using placebos only would unnecessarily prevent other types of investigations that may be scientifically or ethically justified (for example, if there is an available vaccine that ethically precludes use of a placebo). For examples of approaches to designing adequate and well-controlled studies that distinguish the effect of the drug from other influences (such as the placebo effect, change in the course of the disease, or biased observation), see 21 CFR § 314.126. See also Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products; Guidance for Industry, May 1998, https://www.fda.gov/media/71655/download; E10 Choice of Control Group and related issues in Clinical Trials; Guidance for Industry, May 2001, https://www.fda.gov/media/71349/download. Moreover, FDA's existing regulations allow the Agency to place on clinical hold any Phase 2 or Phase 3 trials for which the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives. 21 CFR § 312.42(b)(2)(ii). Because existing FDA regulations provide the Agency with sufficient authority to ensure that inferences can be drawn from Phase 2 and Phase 3 investigational studies, we do not believe there is a need to undertake any rulemaking.

[32] A Phase I/II Study to Determine Efficacy, Safety and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in UK Healthy Adult Volunteers, available at ! https://clinicaltrials.gov/ct2/show/NCT04324606?term=NCT04324606&draw=2&rank=1.

[33] To the extent that Petitioner's request regarding saline injections could be interpreted as a request for FDA to issue a prospective rule that would bind all sponsors of any future Phase 2 or Phase 3 trials for COVID-19 vaccines, we also deny that request. The purpose of control groups is to allow inferences to be drawn from the clinical trial. While in many cases a saline placebo might be an appropriate control, other choices for control groups may sometimes be appropriate and the choice of the control group should be considered in the context of standard therapies, the adequacy of the evidence to support the chosen design, and ethical considerations. See, e.g., E10 Choice of Control Group and related issues in Clinical Trials; Guidance for Industry, May 2001, https://www.fda.gov/media/71349/download. As also stated previously, in the context of investigational studies for COVID-19 vaccines, FDA has stated that if availability of a COVID-19 vaccine proven to be safe and effective precludes ethical inclusion of a placebo control group, that vaccine could serve as the control treatment in a study designed to evaluate efficacy with noninferiority hypothesis testing. See June 2020 Guidance. A regulation that would limit trial designs to using saline injection for placebos would unnecessarily prevent other types of investigations that may be scientifically or ethically justified (for example, if there is an available vaccine that

iii. Opaque Vials

Petitioner's request includes the statement that "[i]f the vaccine and saline are visually distinguishable, opaque vials should be used." CP at 1.

Opaque vials can be used as a mechanism to maintain study blinding in a study in the event that the investigational vaccine and the control are visually different. Blinding is a key technique used to minimize the chance of study bias and ensure that the test treatment and control groups are treated similarly in the course of the study.[34] The type and choice of vials used for a study vaccine and a control is at the discretion of the sponsor and depends on a number of factors, such as the nature of the vaccine and the control and the availability of appropriate vials. If there are differences in the appearance of the study vaccine and the control, study procedures may take this into consideration as necessary to ensure blinding and study integrity (for example, one person might administer the vaccine, and another might query about adverse events). The Petitioner has not provided evidence that, and FDA is currently aware of no other information indicating that, the blinding and integrity of any of the Phase 2 or Phase 3 studies of COVID-19 vaccines under FDA IND have been compromised. The Agency has reviewed the protocol for each of the COVID-19 vaccine INDs and has determined that the design of the current clinical studies, including provisions for blinding at the time of vaccine administration, continue to ensure study integrity. In addition, FDA's regulations allow the Agency to place on clinical hold any Phase 2 or Phase 3 trials for which the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives. 21 CFR § 312.42(b)(2)(ii). If FDA becomes aware of problems with study design, FDA has the authority to address such problems. For this reason, FDA declines to take action based on Petitioner's requests to require any sponsors of studies under FDA IND to change their procedures relating to blinding, including requiring opaque vials. FDA therefore denies Petitioner's request insofar as Petitioner asks FDA to take any action with respect to any Phase 2 or Phase 3 trials under FDA IND regarding the use of opaque vials.[35,36]

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ethically precludes use of a placebo). FDA has a robust process for reviewing INDs and ensuring that Phase 2 and Phase 3 clinical trials are designed in such a way as to allow appropriate inferences to be drawn from the trials. Indeed, FDA's existing regulations allow the Agency to place on clinical hold any Phase 2 or Phase 3 trials for which the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives. 21 CFR § 312.42(b)(2)(ii). Because existing FDA regulations provide the Agency with sufficient authority to ensure that inferences can be drawn from Phase 2 and Phase 3 investigational studies, we do not believe there is a need to undertake any rulemaking.

[34] See, e.g., E10 Choice of Control Group and related issues in Clinical Trials; Guidance for Industry, May 2001, https://www.fda.gov/media/71349/download.

[35] However, if FDA becomes aware of a Phase 2 or Phase 3 trial for which the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives due to problems with blinding, FDA may take action under 21 CFR § 312.42(b)(2)(ii) to place such an investigation on clinical hold. If FDA takes such action, we would do so under FDA's clinical hold authority and not based on the request in the Petition or Amended Petition. The Petition and Amended Petition request an across-the-board approach to clinical trial administration, but FDA's clinical hold authorities require the careful evaluation of individual trials, taking into account the investigation-specific information contained within an IND. We believe that such a case-by-case approach is critical to ensuring the quality and safety of clinical investigations.

[36] To the extent that Petitioner's request can be interpreted as a request for FDA to undertake rulemaking to require the use of opaque vials, FDA also denies this request. Such a rulemaking would impose an across-the-board approach to blinding that may not be scientifically justified when there are other ways to ensure adequate blinding. In addition, as stated previously, FDA regulations provide the Agency with sufficient authority to ensure that

iv. Relative Sizes of Experimental and Control Groups

Petitioner also requests that FDA require that a "placebo control group…be of at least equivalent size to the experimental group." CP at 1.

As clinical development of a COVID-19 vaccine progresses, an adequate body of data is needed to support the safety of vaccinating the proposed study populations and number of participants and, for later stage development, to ensure that the study design is adequate to meet its objectives.[37] Assurance that subject populations are similar in test and control groups is best attained by randomly dividing a single sample population into groups that receive the test or control treatments. Randomization avoids systematic differences between groups with respect to known or unknown baseline variables that could affect outcome.[38] FDA has advised that, in the clinical development of vaccines for the prevention of COVID-19, "[a]n individually randomized controlled trial with 1:1 randomization between vaccine and placebo groups is usually the most efficient study design for demonstrating vaccine efficacy."[39] Following such guidance would result in a study in which the placebo control group would be of equivalent size to the experimental group, as the Petitioner advocates.

However, other types of randomization, such as cluster randomization, may be acceptable. FDA has advised that such types of randomization require careful consideration of potential biases that are usually avoided with individual randomization.[40]

FDA has determined that, at the present time, the design of the Phase 2 and Phase 3 studies under FDA IND, including how the studies provide for the relative numbers of subjects to be enrolled in each arm of the studies, permits comparison of subjects treated with the vaccine candidate with a suitable control population, such that the quality of the scientific evaluation of these vaccines is adequate to permit an evaluation of the vaccines. In addition, FDA's regulations allow the Agency to place on clinical hold any Phase 2 or Phase 3 trials for which the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives. 21 CFR § 312.42(b)(2)(ii). If FDA becomes aware of problems with study design related to randomization, FDA has the authority to address such problems.[41] We therefore do not believe there is a need to take any action based on Petitioner's request with respect to any Phase 2 or

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inferences can be drawn from Phase 2 and Phase 3 investigational studies (see 21 CFR § 312.42(b)(2)(ii)). We therefore do not believe there is a need to undertake any rulemaking related to the use of opaque vials.

[37] June 2020 Guidance at 9.

[38] See E10 Choice of Control Group and Related Issues in Clinical Trials; Guidance for Industry, May 2001, https://www.fda.gov/media/71349/download.

[39] June 2020 Guidance at 12.

[40] Id.

[41] Although the Amended Petition does not request that FDA take any action regarding study size, the Amended Petition does assert the need for a "well-powered trial to assess the safety of the vaccine. . . ." We agree that it is important that clinical trials be of an appropriate size, and we have not authorized—nor will we authorize—any vaccines based on inadequate trials.

Phase 3 trials under FDA IND to require 1:1 randomization between vaccine and placebo groups.[42] Accordingly, we deny Petitioner's request.[43]

b. Adverse Event Documentation

Petitioner asks FDA to require all Phase 2 and 3 studies of vaccines against COVID-19 to document

> [a]ll systemic adverse reactions, adverse events, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue arising or exacerbated post-vaccination…for each subject post-vaccination for a period of at least twelve months for adults, thirty-six months for children and teenagers, and sixty months for infants and toddlers.

CP at 1. Similarly, Petitioner requests that FDA require that, for such studies,

> any and all adverse events and reactions (including, but not limited to, systemic adverse reactions, adverse events, non-serious adverse event [sic], serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue of any degree or type arising or exacerbated post-vaccination, whether suspected, unexpected, expected or otherwise, and whether or not considered related to the vaccine) be documented for the entire duration of the clinical trial

(Amended CP at 1) and that, for Phase 2 and Phase 3 trials, "all adverse events and reactions for each subject be tracked post-vaccination for a minimum period of twelve months for adults, thirty-six months for children, and sixty months for infants and toddlers." Amended CP at 2.

Because the Petition and Amended Petition refer to adverse event monitoring in the context of Phase 2 and Phase 3 trials, it appears that the requests related to adverse event monitoring seek the specified adverse event monitoring during the clinical trial period. FDA agrees that safety monitoring is a critical feature of the vaccine development process, and FDA will not authorize or license a vaccine that has not been shown to meet the relevant statutory requirements. However, for the reasons explained below, we do not agree that FDA must require that the clinical trials for a vaccine provide the specified adverse event monitoring.

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[42] However, if FDA becomes aware of a Phase 2 or Phase 3 trial for which the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives due to problems with randomization, FDA may take action under 21 CFR § 312.42(b)(2)(ii) to place such an investigation on clinical hold. If FDA takes such action, we would do so under FDA's clinical hold authority and not based on the Petitioner's request. Petitioner requests an across-the-board approach to clinical trial administration, but FDA's clinical hold authorities require the careful evaluation of individual trials taking into account the investigation-specific information contained within an IND. We believe that such a case-by-case approach is critical to ensuring the quality and safety of clinical investigations.

[43] To the extent that Petitioner's request can be interpreted as a request for FDA to undertake rulemaking to require the use of 1:1 randomization, FDA also denies this request. As stated previously, FDA regulations provide the Agency with sufficient authority to ensure that inferences can be drawn from Phase 2 and Phase 3 investigational studies (see 21 CFR § 312.42(b)(2)(ii)). There may be more than one appropriate way to develop a randomization scheme that protects against the possibility that differences between groups at baseline will lead to outcome differences that might mistakenly be attributed to the therapeutic effect. See Good Review Practice: Clinical Review of Investigational New Drug Applications (describing different randomization schemes), December 2013, https://www.fda.gov/media/87621/download. Any rulemaking to require 1:1 randomization would preclude other clinical trial designs that may be scientifically justified. We therefore do not believe there is a need to undertake any rulemaking, and that doing so could have the negative consequence of limiting sponsors' ability to develop clinical trials that are appropriately tailored to scientific needs.

With respect to FDA licensure of a COVID-19 vaccine, FDA addressed this topic in the June 2020 Guidance. In that guidance, FDA specifically addresses safety considerations in the development of such vaccines, and advises that "[t]he general safety evaluation of COVID-19 vaccines, including the size of the safety database to support vaccine licensure, should be no different than for other preventive vaccines for infectious diseases."[44] FDA recommends that, throughout clinical development of COVID-19 vaccines, safety assessments should include:

- Solicited local and systemic adverse events for at least 7 days after each study vaccination in an adequate number of study participants to characterize reactogenicity (including at least a subset of participants in late phase efficacy trials).
- Unsolicited adverse events in all study participants for at least 21-28 days after each study vaccination.
- Serious and other medically attended adverse events in all study participants for at least 6 months after completion of all study vaccinations. Longer safety monitoring may be warranted for certain vaccine platforms (e.g., those that include novel adjuvants).

June 2020 Guidance at 15.

With respect to the EUA of a COVID-19 vaccine, in October 2020, FDA addressed this topic in the October 2020 Guidance. In this guidance, FDA provides recommendations regarding the safety and effectiveness information that should be included in an EUA request for a COVID-19 vaccine. FDA states in this guidance that the Agency does not expect to be able to make a favorable benefit-risk determination that would support an EUA without Phase 3 data that include the following, which would help the Agency to assess the safety of the vaccine.

- Local and systemic solicited adverse reactions collected for the protocol-defined duration of follow-up in an adequate number of subjects to characterize reactogenicity in each protocol-defined age cohort participating in the trial;
- All safety data collected up to the point at which the database is locked to prepare the submission of the EUA request, including a high proportion of enrolled subjects (numbering well over 3,000 vaccine recipients) followed for serious adverse events (SAEs) and adverse events of special interest for at least one month after completion of the full vaccination regimen; and
- Sufficient cases of severe COVID-19 among study subjects to support low risk for vaccine-induced enhanced respiratory disease (ERD) (a total of 5 or more severe COVID-19 cases in the placebo group would generally be sufficient to assess whether the severe COVID-19 case split between vaccine vs. placebo groups supports a favorable benefit-risk profile or conversely raises a concern about ERD).

October 2020 Guidance at 10.

A robust safety database is always important to accurately assess and adequately characterize the risks of a new drug, including a new vaccine. Sponsors collect extensive safety-related data throughout the course of vaccine development, and knowledge about a vaccine's safety profile continually evolves as safety data accumulate.

i. Petitioner's Requests to Document All Adverse Events

With regard to Petitioner's request that

> any and all adverse events and reactions (including, but not limited to, systemic adverse reactions, adverse events, non-serious adverse event [sic], serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health

[44] Id. at 15.

> issue of any degree or type arising or exacerbated post-vaccination, whether suspected, unexpected, expected or otherwise, and whether or not considered related to the vaccine) be documented

(Amended CP at 1) and assertion that "[g]iven that 'serious adverse events' are already being captured for 6 months, it appears foolhardy to not also capture all adverse events," (Amended CP at 4) we point out that doing so would result in the collection of information that would not necessarily be of value in assessing the safety of the vaccine candidate.

It should be noted that FDA has reviewed the ongoing COVID-19 vaccine INDs to ensure that subjects are adequately monitored for the occurrence of adverse events. (Robust safety monitoring is standard practice in clinical studies of vaccines).[45]

FDA's policy is that in clinical trials certain types of safety data should always be collected, including data on all serious adverse events; data on non-serious adverse events that lead to dose modification, drug discontinuation, or withdrawal from the study; and data on unscheduled study visits, hospitalizations, and accidental injuries because these events may reflect serious adverse events of the drug.[46] For these types of safety data, it is generally important to collect information on all occurrences to better understand causality, incidence, severity of adverse events, populations that are at risk, dose-response, and other factors that contribute to our understanding of the nature of the event and who is at risk.[47] FDA's IND regulations also specify reporting requirements for certain adverse events; for example, 21 CFR § 312.32(c)(1)(i) requires expedited reporting of serious, unexpected suspected adverse reactions to FDA and all investigators during drug development.

Data safety monitoring boards (DSMBs) can also play a role in the monitoring of safety signals in clinical trials. DSMBs are groups of individuals with pertinent expertise that review, on a regular basis, accumulating data from ongoing clinical trials.[48] For COVID-19 vaccine trials, FDA specifically recommends that sponsors periodically monitor for unfavorable imbalances between vaccine and control groups in COVID-19 disease outcomes, and recommends the use of an independent DSMB for safety signal monitoring, especially during later-stage development.[49]

Comprehensive safety data, including essentially all adverse events, are collected in the early stages of drug development.[50] In the later stages of premarket development, however, it may be appropriate to use a selective approach to safety data collection for common, non-serious adverse events that have already been well-characterized through data collection in earlier stages. For example, if safety data already collected on hundreds of patients indicate that 17 percent reported a headache after receiving a drug, compared with 10 percent receiving placebo, collection of similar data in thousands of additional patients in a large phase 3 study would minimally refine

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[45] World Health Organization (WHO), Guidelines on clinical evaluation of vaccines: regulatory expectations, June 2017, https://www.who.int/biologicals/expert_committee/WHO_TRS_1004_web_Annex_9.pdf?ua=1.
[46] Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations; Guidance for Industry, February 2016, at 6, https://www.fda.gov/media/82664/download.
[47] Id. at 7.
[48] See Establishment and Operation of Clinical Trial Data Monitoring Committees; Guidance for Clinical Trial Sponsors, March 2006, https://www.fda.gov/media/75398/download.
[49] June 2020 Guidance at 15.
[50] Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations; Guidance for Industry, February 2016, at 2, https://www.fda.gov/media/82664/download.

this value and would require extensive resource utilization, while providing no important new information.[51]

The indiscriminate collection of data that do not contribute to better characterizing the safety profile of a vaccine may actually have negative consequences for the clinical development of the vaccine. Reporting of all adverse events, for the entire duration of a clinical study, including those for which there is little reason to believe that a vaccine caused the event, may complicate or delay FDA's ability to detect an important safety signal. A focus on the documentation and reporting of selected adverse events, including those that are serious, and those for which causality is scientifically plausible, minimizes reports that do not contribute to FDA's understanding of the developing safety profile of a vaccine and decreases the number of uninterpretable reports ("noise") in the system. Selective safety data collection in late-stage premarket clinical investigations is consistent with FDA's overall approach to safety assessment, which focuses on information that is useful and adds to existing knowledge.[52]

In addition, excessive safety data collection may have negative consequences for the clinical development of the vaccine. In contrast, a carefully-structured collection of safety data for a reasonable and scientifically-informed period of time may facilitate the conduct of larger studies without compromising the integrity and the validity of study results or losing important information, facilitate patients' participation in clinical studies, and help contain costs by making more-efficient use of clinical study resources. For these reasons, selective safety data collection may be appropriate and, in fact, preferable from a scientific standpoint to the indiscriminate collection of information in clinical trials.

ii. Petitioner's Requests to Document Adverse Events for Specified Periods of Time

A decision about the appropriate length of safety studies is based on various factors, including the intended use of the product, the nature of the labeled patient population, and earlier clinical and preclinical safety assessments.[53] As described in the June 2020 Guidance, FDA has stated an expectation that all study participants enrolled in COVID-19 clinical studies be monitored for the occurrence of serious and other medically attended adverse events for at least 6 months after completion of all study vaccinations.

In order to issue an EUA, the FDA must determine, among other things, that the known and potential benefits of a product outweigh its known and potential risks and that the product may be effective in preventing, diagnosing, or treating serious or life-threatening diseases or conditions caused by the agent or agents identified in the EUA declaration. A favorable benefit–risk determination cannot be made for vaccines that might have only modest benefit or for which there are insufficient data to assess the safety profile. FDA's October 2020 Guidance recommends that, to support an EUA for a COVID-19 vaccine, data from Phase 3 studies (which may result from a protocol-specified interim analysis) include a median follow-up duration of at least 2 months after completion of the full vaccination regimen.[54] FDA's October 2020

[51] Id.
[52] Id. at 3.
[53] Premarketing Risk Assessment; Guidance for Industry, March 2005 at 9; https://www.fda.gov/media/71650/download.
[54] October 2020 Guidance at 10.

Guidance reflects the Agency's assessment that, from a safety perspective, a 2-month median follow-up after completion of the full vaccination regimen (meaning that at least half of vaccine recipients in clinical trials have at least 2 months of follow-up) will allow identification of potential adverse events that were not apparent in the immediate postvaccination period.[55] Adverse events considered plausibly linked to vaccination generally start within 6 weeks after vaccine receipt.[56] Two months of follow-up should, therefore, provide time for potential immune-mediated adverse events that began within this 6-week period to be observed and evaluated.

For an EUA for a COVID-19 vaccine, FDA's recommendation for a median follow-up period of at least 2 months after the final vaccine dose is based on extensive historical experience with vaccines, the need for a vaccine to address the current pandemic, and the magnitude of vaccine effectiveness that will be required to support a favorable benefit-risk profile for use of a COVID-19 vaccine under an EUA.[57] We note that the Phase 3 data would also be complemented by Phase 1 and 2 data, which would be of a longer duration than safety data available from the Phase 3 trial at the time of EUA request submission.

Regarding the request in the Petition and Amended Petition that Phase 2 and 3 trials track adverse events for 12 months for adults, for the reasons described above, we do not believe that such a follow-up is needed to support EUA for a COVID-19 vaccine at this time. For example, we believe that an EUA is justified for the Pfizer-BioNTech COVID-19 Vaccine,[58] and we are issuing an EUA for the Pfizer-BioNTech COVID-19 Vaccine, which is supported by information from participants in the Phase 2/3 population who were followed for safety for a median of two months after receiving the second dose.[59,60] This follow-up period is justified based on the need for a vaccine to address the current pandemic and the magnitude of vaccine effectiveness that was demonstrated to support the favorable benefit-risk profile for the use of the vaccine under

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[55] Id.

[56] Health Resources and Services Administration, Vaccine Injury Table, 2017, https://www.hrsa.gov/sites/default/files/vaccinecompensation/vaccineinjurytable.pdf.

[57] For the EUA for BNT162b, FDA has determined, based on the scientific data and information available for BNT162b, that there is adequate evidence for the authorization. For more information about the basis for FDA's determination, see FDA Briefing Document, Pfizer-BioNTech COVID-19 Vaccine, Vaccines and Related Biological Products Advisory Committee Meeting, December 10, 2020 (FDA's Pfizer-BioNTech COVID-19 Vaccine Briefing Document), https://www.fda.gov/media/144245/download.

[58] For more detailed information about the safety data for BNT162b, see FDA's Pfizer-BioNTech COVID-19 Vaccine Briefing Document, https://www.fda.gov/media/144245/download.

[59] EUA letter for Pfizer-BioNTech COVID-19 Vaccine dated December 11, 2020, https://www.fda.gov/media/144412/download.

[60] In addition to the information from the BNT162b vaccine clinical trial, FDA has also considered post-market information about the product based on the product's prior authorization in the United Kingdom. Anaphylactic reactions in the immediate post-vaccination period have occurred with use of the vaccine in the United Kingdom in two individuals. The component(s) of the vaccine that may have triggered these anaphylactic reactions are unknown at this time. FDA has considered these events as part of the Agency's safety review, and has determined that the risk of allergic reactions can be managed post-authorization. The Fact Sheets and Prescribing Information for the Pfizer-BioNTech COVID-19 Vaccine include a contraindication for use in individuals with known allergy to any component of the vaccine, as well as information on the potential for severe allergic reactions and the need for vaccine providers to be able to manage them should they occur. See FDA's website information regarding the authorization. Additionally, risk of anaphylaxis will be further evaluated as part of the pharmacovigilance plan for the Pfizer-BioNTech COVID-19 Vaccine.

EUA. Therefore, we deny the request to require a 12-month follow-up period for adults, and we do not believe this must be a condition of vaccine authorization.[61]

Insofar as the Petition and Amended Petition ask that FDA require, at this time, that Phase 2 and 3 trials track adverse events for 36 months for children and teenagers, and 60 months for infants and toddlers, we also deny this request. FDA does not intend to authorize or license any COVID-19 vaccine until the relevant statutory requirements have been met for the population indicated in the labeling. FDA intends to consider the appropriate safety follow-up period for pediatric populations based on the available scientific data and information for a specific investigational vaccine.

We also conclude that Petitioner has not provided scientific support for the requested pediatric safety-follow up period. The Petitioner relies on a 2019 publication authored by researchers at the FDA and Duke University that described the duration of drug therapy in completed drug trials that supported approval for use of the drugs in children with chronic diseases. Amended CP at 5. We point out, however, that vaccine clinical studies were excluded from the analysis. It is not scientifically appropriate to extrapolate the results or conclusions from this study to vaccines, as vaccines for bacterial or viral infectious diseases are given episodically over an individual's lifespan and are not chronically or more frequently administered, as occurs with some drugs or biologics. Therefore, the research that Petitioner cites for the requested pediatric safety follow-up period does not support the action requested.

With respect to the Petitioner's request that all adverse events be documented for the entire duration of the COVID-19 vaccine clinical trials, we point out that this, too would result in the collection of information that would not be of value in assessing the safety of the vaccine. As the duration of any reporting period increases, more events occur that are unrelated to the vaccine; this increases the "noise" in the system and may complicate FDA's determination of the safety profile of the vaccine. In addition, excessive safety data collection may have negative consequences for the clinical development of the vaccine. A carefully-structured collection of safety data for a reasonable and scientifically-informed period of time, however, may facilitate the conduct of larger studies without compromising the integrity and the validity of study results

[61] To the extent that the Petition's and Amended Petition's request for 12-month adult adverse event monitoring in Phase 2 and 3 trials can be interpreted to request that FDA require changes to the plans or protocols for the ongoing trials under FDA IND that are not the subject of an EUA, we also deny this request. The ongoing trials may be used to support EUA requests, and for the reasons articulated in the main text of this letter, FDA believes that shorter follow-up periods may be justified to support EUAs based on the need for a vaccine to address the current pandemic, and the magnitude of vaccine effectiveness that would be demonstrated to support the favorable benefit–risk profile for the use of the vaccine under EUA. Because Petitioner's requested follow-up period may not be needed to justify an EUA for a COVID-19 vaccine, we decline to require changes to the follow-up procedures outlined in the protocols for products that are under INDs and that are not yet the subject of EUAs. We also decline to take action based on the Petition for the additional reason that FDA regulations provide the Agency with sufficient authority to ensure that inferences can be drawn from Phase 2 and Phase 3 investigational studies (see 21 CFR § 312.42(b)(2)(ii)). If there are problems with the safety follow-up procedures in ongoing trials, FDA's regulations provide a basis for FDA to address such problems. Petitioner requests an across-the-board approach to clinical trial administration, but FDA's clinical hold authorities more appropriately require the careful evaluation of individual trials taking into account the investigation-specific information contained within a particular IND.

or losing important information, facilitate patients' participation in clinical studies, and help contain costs by making more-efficient use of clinical study resources.[62]

For any vaccine, regardless of the length of pre-licensure safety studies, safety continues to be evaluated post-licensure. For a vaccine to prevent COVID-19, FDA recommends early planning of pharmacovigilance activities, the specifics of which will depend on the safety profile of the vaccine and will be based on the pre-licensure clinical safety database, preclinical data, and available safety information for related vaccines, among other considerations.[63] FDA's June 2020 Guidance advises that follow-up of study participants for COVID-19 outcomes should continue as long as feasible, ideally at least one to two years.[64] FDA's guidance document states that the Agency may recommend that pharmacovigilance activities for vaccines to prevent COVID-19 include submission of reports of specific adverse events of interest in an expedited manner beyond routine required reporting; submission of adverse event report summaries at more frequent intervals than specified for routine required reporting; and a pharmacoepidemiologic study to further valuate important identified or potential risks from the clinical development program, such as uncommon or delayed-onset adverse events of special interest.[65]

For these reasons, FDA denies Petitioner's requests to require all Phase 2 and Phase 3 studies of vaccines against COVID-19 to document all adverse events for each subject post-vaccination for the requested periods of time prior to authorization.

2. Petitioner's Requests Relating to Guidance

In the Amended CP, Petitioner makes certain requests relating to FDA's June 2020 Guidance.

a. Number of Subjects in Clinical Studies

Petitioner requests that

> [f]or Phase III trials of COVID-19 vaccines…more specific and appropriate guidance on the number of subjects receiving the vaccine and placebo be provided in the [June 2020 Guidance], and that the updated guidance require at least 20,000 subjects receive the COVID-19 vaccine with a 1:1 randomization between vaccine and placebo groups.

Amended CP at 2.[66,67]

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[62] Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations; Guidance for Industry, February 2016, at 3, https://www.fda.gov/media/82664/download.
[63] June 2020 Guidance at 16.
[64] Id. at 12.
[65] Id. at 16-17.
[66] Petitioner appears to limit this request to "Phase III trials of COVID-19 vaccines." Insofar as Petitioner intended this to apply to a larger group of studies, our response below extends to Phase 2 and Phase 3 studies.
[67] We note that, at the time Petitioner submitted the Amended Petition, FDA had published its June 2020 Guidance on COVID-19 vaccine development but had not yet published the October 2020 Guidance. We interpret this request related to updating FDA's guidance document as requesting changes to either or both guidance documents, because the objective of this aspect of the Amended Petition is that FDA provide the guidance that Petitioner requests.

As stated above, FDA has advised that "[t]he general safety evaluation of COVID-19 vaccines, including the size of the safety database to support vaccine licensure, should be no different than for other preventive vaccines for infectious diseases."[68] FDA has also advised that

> [t]he pre-licensure safety database for preventive vaccines for infectious diseases typically consists of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure. FDA anticipates that adequately powered efficacy trials for COVID-9 vaccines will be of sufficient size to provide an acceptable safety database for each of younger adult and elderly populations, provided that no significant safety concerns arise during clinical development that would warrant further pre-licensure evaluation.

June 2020 Guidance at 15.

As discussed in section III.B.1.a.iv, as clinical development of a COVID-19 vaccine progresses, an adequate body of data is needed to support the safety of vaccinating the proposed study populations and number of participants and, for later stage development, to ensure that the study design is adequate to meet its objectives.[69] What constitutes an adequate body of data for a vaccine in development will generally depend on a number of factors, including the nature of a particular vaccine; its intended use; and information, including nonclinical data, gathered and analyzed before clinical studies are begun. The data needs for a specific clinical study are taken into account when the study is designed and may affect the numbers of subjects assigned to control and treatment groups and the randomization ratio.

Because the optimal study design of a Phase 2 or Phase 3 clinical study for a COVID-19 vaccine candidate is determined by numerous factors dependent on the data needs specific to the particular candidate, FDA denies Petitioner's request to revise the June 2020 Guidance to specify that a particular number of subjects be assigned to the experimental arm with a 1:1 randomization between vaccine and placebo groups.[70] We believe that FDA's existing guidance strikes an appropriate balance of recommending 1:1 randomization, while also acknowledging that other type of randomization, such as cluster randomization, may also be acceptable in some circumstances.[71] We also believe that the Agency's existing guidance already addresses the importance of adequately sized study groups.[72] Therefore, we do not agree with Petitioner that

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[68] June 2020 Guidance at 15.

[69] Id at 9.

[70] To the extent that Petitioner's request regarding changes to FDA's guidance reflects a concern that FDA would authorize a COVID-19 vaccine based on data from an inadequately powered clinical trial, we note that the EUA for Pfizer-BioNTech COVID-19 Vaccine followed a Phase 1/2/3 clinical trial that has enrolled approximately 44,000 participants. At the time of the analysis for the EUA, approximately 37,600 participants have been followed for a median of 2 months after the last dose of vaccine or placebo. See FDA's website information regarding the authorization.

[71] As stated previously, there may be more than one appropriate way to develop a randomization scheme that protects against the possibility that differences between groups at baseline will lead to outcome differences that might mistakenly be attributed to the therapeutic effect. See Good Review Practice: Clinical Review of Investigational New Drug Applications (describing different randomization schemes), December 2013, https://www.fda.gov/media/87621/download.

[72] "Study sample sizes and timing of interim analyses should be based on the statistical success criteria for primary and secondary (if applicable) efficacy analyses and realistic, data-driven estimates of vaccine efficacy and incidence of COVID-19 (or SARS-CoV-2 infection) for the populations and locales in which the trial will be conducted" (June 2020 Guidance at 14); "The general safety evaluation of COVID-19 vaccines, including the size of the safety

changes are needed to the Agency's guidance to address randomization and study size concerns. Finally, because the Amended CP asks that FDA issue an updated guidance that would "require" the 1:1 randomization and 20,000 study subjects, we note that FDA's guidance process is not designed to "require" anything. FDA guidance documents are non-binding and represent FDA's current thinking on a subject.[73] FDA staff and regulated persons may use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.[74] For FDA to issue generally-applicable requirements, the Agency is generally required to follow notice-and-comment rulemaking procedures. 5 U.S.C. § 553. Petitioner's request that FDA "require" certain study design features in guidance is therefore not legally supportable.

For all of these reasons, FDA denies Petitioner's request that FDA update its guidance to "require at least 20,000 subjects receive the COVID-19 vaccine with a 1:1 randomization between vaccine and placebo groups."

b. Converting Guidance to Regulatory Requirements

Petitioner requests that FDA "formally adopt [the June 2020 Guidance], with the necessary flexibility, as formal regulatory requirements." Amended CP at 2. We interpret this to be a request that FDA promulgate regulations codifying the recommendations in the June 2020 Guidance.

The Petitioner is correct in understanding that the June 2020 Guidance does not impose regulatory requirements. FDA's guidance documents are prepared for FDA staff, applicants/sponsors, and the public; and describe the FDA's interpretation of or policy on a regulatory issue. They represent FDA's current thinking on a topic, but do not establish any rights for any person and generally do not operate to bind FDA or the public. Alternative approaches to those discussed in guidance documents can be used if those approaches satisfy the requirements of the applicable statutes and regulations.[75]

The recommendations in the June 2020 Guidance are expected to assist sponsors in the clinical development and licensure of vaccines for the prevention of COVID-19. In that guidance, FDA describes its current recommendations regarding the data needed to facilitate clinical development and licensure of such vaccines.[76] It provides an overview of key considerations to satisfy regulatory requirements set forth in the IND regulations in 21 CFR Part 312 and licensing regulations in 21 CFR Part 601 for, among other things, clinical data through development and licensure, and for post-licensure safety evaluation of such vaccines. As Petitioner notes, the June 2020 Guidance addresses some of the issues raised by the Petitioner, including the use of

database to support vaccine licensure, should be no different than for other preventive vaccines for infectious diseases" (June 2020 Guidance at 15); "FDA anticipates that adequately powered efficacy trials for COVID-19 vaccines will be of sufficient size to provide an acceptable safety database for each of younger adult and elderly populations, provided that no significant safety concerns arise during clinical development that would warrant further pre-licensure evaluation" (June 2020 Guidance at 15; October 2020 Guidance FN. 5).

[73] See 21 CFR § 10.115(b) (providing that "Guidance documents are documents prepared for FDA staff, applicants/sponsors, and the public that describe the Agency's interpretation of or policy on a regulatory issue."

[74] See 21 CFR § 10.115(d) (providing that "Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA.").

[75] See 21 CFR § 10.115.

[76] June 2020 Guidance at 2.

randomized, double-blinded, and placebo-controlled later-phase studies with randomization between vaccine and placebo groups. Amended CP at 2.

FDA disagrees with Petitioner's view that the recommendations in the June 2020 Guidance should be codified in legally-binding regulations.

It is important to note that sponsors are legally required to submit an IND to FDA in advance of commencing clinical studies in the U.S. 21 U.S.C. § 355(i); 21 CFR § 312.40. FDA reviews all INDs to assure the safety and rights of subjects and, in Phase 2 and 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 has the authority to delay a proposed clinical investigation or suspend an ongoing investigation by imposing a clinical hold on a study if certain grounds apply, including grounds relating to the safety of the study participants. 21 CFR § 312.42(b). (For further discussion of clinical holds, see section III.A..) Additional regulations are not necessary to enable FDA to take action should any safety or study quality concerns arise before or during a clinical study of a COVID-19 vaccine candidate.

Finally, FDA agrees with Petitioner that flexibility can be necessary in some aspects of vaccine regulation. Regulations generally take years to develop using notice-and-comment procedures; once effective, they are time and resource intensive to modify. Therefore, regulations are typically appropriate when it is unlikely that there will be scientific developments that may affect the appropriateness of the regulation. However, the scientific understanding of the SARS-CoV-2 novel coronavirus and COVID-19 pathogenesis continues to evolve in a way that is not conducive to the Agency's issuing binding regulations specific to COVID-19 vaccines. New data and information continue to emerge regarding SARS-CoV-2 pathogenesis, COVID-19, and COVID-19 vaccines. It is FDA's policy judgment that, in light of the rapidly developing state of knowledge in this area, a guidance document conveying the Agency's current thinking on issues relating to COVID-19 vaccine development is more appropriate and useful at this time than a binding regulation on those issues would be. Furthermore, FDA's oversight of clinical trials (described elsewhere in this response) already provides the Agency with sufficient authority to monitor for safety and quality issues with clinical trials. In addition, FDA follows a science-based decision-making process to assure that any vaccine that is authorized or licensed meets our standards for safety and effectiveness. Because we do not agree that regulations related to COVID-19 vaccine licensure are warranted, we deny this aspect of the Amended Petition.

C. The Petitions for Stay of Action

In the PSA and Amended PSA,[77] Petitioner requests "[a] stay of the approval of the application for any Phase II and III trials of vaccines against COVID-19, including for ChAdOx1 nCoV-19, that do not include a placebo control group (i.e., a placebo comparator group)"[78] until the following conditions are met:

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[77] There is significant overlap between the PSA and Amended PSA. Both documents request "[a] stay of the approval of the application for any Phase II and III trials of vaccines against COVID-19, including for ChAdOx1 nCoV-19, that do not include a placebo control group (i.e., a placebo comparator group)" until the first three conditions in the numbered list in section III.C satisfied. The Amended PSA is different in that it also requests that the fourth condition in the numbered list be satisfied and identifies a broader "decision involved."

[78] Petitioner submitted an additional citizen petition (docket number FDA-2020-P-1768) and petition for stay of action (docket number FDA-2020-P-1768) specifically addressing the clinical study for "ChAdOx1 nCoV-19

> 1) the study design for the trial is amended to include a placebo control group (i.e., a placebo comparator group);
>
> 2) the placebo is specified as a saline injection and, if visually distinguishable from the vaccine, both should be packaged in opaque vials;
>
> 3) the placebo control group is of at least equivalent size to the experimental group; and
>
> 4) all systemic adverse reactions, adverse events, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue arising or exacerbated post-vaccination are to be documented for each subject post-vaccination for a period of at least twelve months for adults, thirty-six months for children and teenagers, and sixty months for infants and toddlers.

Amended PSA at 1.[79]

1. Criteria for Granting an Administrative Stay of Action

We do not agree that the requests in the petitions for stay are appropriate for petitions submitted under 21 CFR § 10.35. Petitioner's PSA and Amended PSA seek 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 petitions for stay do meet the threshold requirements in section 10.35, we describe the substantive issues raised by Petitioner 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.

21 CFR § 10.35(e).

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).

(NCT04400838)"; we will address many of Petitioner's requests that are specifically directed to that study in a separate response, based on the requests in the other petition. However, because the requests in the PSA and Amended PSA appear to apply to all COVID-19 vaccines that are in Phase 2 or Phase 3 clinical trials, this response also addresses any Phase 2 or Phase 3 study that may be the subject of other petitions submitted by Petitioner.

[79] Because all of the elements of the PSA are included in the Amended PSA, we refer only to the Amended PSA in this section of our response.

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 and Amended PSA are not frivolous and are 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 and Amended 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 otherwise suffer irreparable injury. Petitioner's argument is that "once the FDA licenses a 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* (*Citizen's Petition* ¶¶ 2-8)." PSA at 2; Amended PSA at 2.[80] Petitioner also asserts that "if the vaccine is licensed without a placebo control group now, ethical considerations may prevent such a placebo-controlled study post-licensure, thereby preventing any such study from ever occurring. (*Citizen's Petition* ¶ 5.)" PSA at 2; Amended PSA at 2.

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 and Amended PSA do not seek a stay of any FDA decision that will force any individuals to receive vaccines. Petitioner seeks a stay of Phase 2 and Phase 3 clinical trials but has not demonstrated that the continuation of the trials will cause States to issue requirements that will in turn cause Petitioner to be vaccinated against Petitioner's will. Indeed, 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 professional body makes any potential decisions regarding mandatory vaccination.[81] The continuation of clinical trials, alone, will not cause the asserted harm. Furthermore, Petitioner has not identified any specific problems with specific clinical trials under FDA IND.[82]

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

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[80] Petitioner states that "[t]he undersigned hereby incorporates by reference as if fully set forth herein the Statement of Grounds from its Citizen's Petition submitted simultaneously with this request." PSA at 1; Amended PSA at 2. We interpret Petitioner's reference here to "*Citizen's Petition*" to refer to Petitioner's citizen petition dated June 17, 2020, because at the time the PSA was submitted that was the only citizen petition that had been submitted on behalf of Petitioner related to COVID-19 vaccine trials. Petitioner has subsequently submitted additional petitions.

[81] 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.

[82] In the CP, Petitioner asserted supposed problems related to alleged lack of use of saline placebo with a clinical trial for ChAdOx1n CoV-19. However, as stated previously, it appears that the study that Petitioner refers to (NCT04324606 on ClinicalTrials.gov) is not one for which FDA has an oversight role.

Petitioner also asserts that sound public policy grounds support a stay because "[r]equiring a placebo control group for the trials of a vaccine where no vaccine exists for the target infection is well supported by the sound public policy detailed in the FDA's own guidance documents. (*Citizen's Petition* ¶¶ 2-7.)" PSA at 2; Amended PSA at 2.

We do not agree that Petitioner has demonstrated sound public policy grounds supporting a stay. Petitioner seeks a stay of Phase 2 and Phase 3 clinical trials. 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 sound public policy requires us to only stay (or issue holds on) clinical trials 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 weighs strongly in favor of the requested relief because using a placebo control (i) will comport with the best scientific practices, (ii) increase public confidence in the safety and efficacy of a product expected to be mandated, and (iii) using a non-inert substance as a control will have the opposite result in that it will create uncertainties regarding the safety of the COVID19 vaccine. (*Citizen's Petition* 2-12.)

PSA at 2; Amended PSA at 2.

Petitioner's assertions with regard to the criterion for a stay of action in 21 CFR § 10.35(e)(4) refers only to the use of placebo controls. We assume Petitioner also believes that there is public health or public interest merit in the other conditions of the PSA and Amended PSA being satisfied. Either way, we conclude that Petitioner has not demonstrated that delay would not be outweighed by public health or other public interests.

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.[83]

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

[83] For a vaccine licensed under BLA, those standards are described in section II.A and Appendix I. For a vaccine with an EUA, those standards are described in section II.B.

identified a single basis for FDA to stay (or place on hold) any clinical trials under FDA IND.[84]

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 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

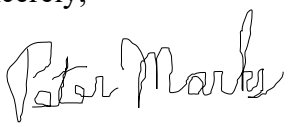
Section 10.35 also provides that FDA may grant a stay of administrative action if the Agency believes it is in the public interest and in the interest of justice. As discussed above, we do not agree that a stay is in the public interest or the interest of justice at this time. It is in the public interest 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) 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 and Amended PSA are denied.

IV. Conclusion

FDA has considered Petitioner's requests as they relate to Phase 2 and Phase 3 studies of vaccines to prevent COVID-19 under IND. For the reasons given in this letter, FDA denies the requests in Petitioner's citizen petitions and also denies the requests in the petitions for stay. Therefore, we deny the Petitions in their entirety.

Sincerely,



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

cc: Dockets Management Staff

[84] See discussion in section III.C.1.b 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.

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 21 CFR § 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)[85] 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]."[86]

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 of a vaccine's ingredients 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.

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

[86] 21 CFR § 601.4(a).

Appendix II: Aspects of Vaccine Postmarketing Safety Monitoring

Post-marketing surveillance of vaccine safety is crucial to detect any rare, serious, or unexpected adverse events, as well as to monitor vaccine lots. Manufacturers often conduct post-marketing observational studies. However, FDA also uses multiple tools and databases to evaluate the safety of vaccines after they have been licensed and used in the general population.

The Vaccine Adverse Event Reporting System (VAERS) is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed in the United States (U.S.). VAERS is co-administered by the FDA and the Centers for Disease Control and Prevention (CDC). Anyone can make a report to VAERS, including vaccine manufacturers, private practitioners, State and local public health clinics, vaccine recipients, and their parents or caregivers. Surveillance programs like VAERS perform a critical function by generating signals of potential problems that may warrant further investigation.

It is often difficult to determine with certainty if a vaccine caused an adverse event reported to VAERS. Many events that occur after vaccination can happen by chance alone. Some adverse events are so rare that their association with a vaccine is difficult to evaluate. In addition, VAERS often receives reports where there is no clear clinical diagnosis. FDA draws upon multiple sources of data and medical and scientific expertise to assess the potential strength of association between a vaccine and a possible adverse event.

Monitoring and analysis of VAERS reports typically includes daily in-depth medical review of all serious reports, statistical data mining techniques, and epidemiological analysis. We look for patterns and similarities in the onset timing and clinical description. We review published literature to understand possible biologic hypotheses that could plausibly link the reported adverse event to the vaccine. We review the pre-licensure data and any other post-marketing studies that have been conducted. We also consider "background rate," meaning the rate at which a type of adverse event occurs in the unvaccinated general population. When necessary, we discuss the potential adverse event with our federal and international safety surveillance partners. We also carefully evaluate unusual or unexpected reports, as well as reports of "positive re-challenges" (adverse events that occur in the same patient after each dose received). When there is sufficient evidence for a potential safety concern we may proceed to conduct large studies, and we may coordinate with our federal, academic and private partners to further assess the potential risk after vaccination. In addition, when potential safety issues arise, they are often presented to various U.S. government advisory committees, including the Vaccines and Related Biological Products Advisory Committee, the Advisory Committee on Immunization Practices, the Vaccines Advisory Committee, and the Advisory Committee on Childhood Vaccines, and are often discussed with experts from other countries and from the World Health Organization (WHO). Federal agencies that assist in population-based vaccines safety studies include the Centers for Medicaid and Medicare (CMS), the Department of Defense (DoD), and the Indian Health Services (IHS). In addition, we generally communicate and work with international regulatory authorities and international partners to conduct studies in vaccine safety.

The Vaccine Safety Datalink (VSD) project has actively monitored vaccine safety in more than 9.1 million people nationwide, over 3% of the U.S. population. The VSD can monitor vaccine safety with near real-time surveillance systems, which is particularly important for new vaccines. If there is a vaccine safety signal in the VSD, chart reviews and case series analyses are done

when assessing the possible association between a vaccine and an adverse event. If needed, VSD is able to use its large health care database to further evaluate specific vaccine safety concerns.

The Clinical Immunization Safety Assessment (CISA) is a national network of six medical research centers with expertise conducting clinical research related to vaccine safety. The goals of CISA are: to study the pathophysiologic basis of adverse events following immunization using hypothesis-driven protocols; to study risk factors associated with developing an adverse event following immunization using hypothesis-driven protocols, including genetic host-risk factors; to provide clinicians with evidence-based guidelines when evaluating adverse events following immunization; to provide clinicians with evidence-based vaccination or revaccination guidelines; and to serve as a regional referral center to address complex vaccine safety inquiries. Advances in genetics and immunology continue to help us further assess the safety of vaccines, and FDA has established a genomics evaluation team for vaccine safety.

Finally, the Sentinel Initiative is a national electronic system that will continue to improve FDA's ability to track the safety of medical products, including vaccines. Launched in May 2008 by FDA, the Sentinel System will enable FDA to actively query diverse automated healthcare data holders – like electronic health record systems, administrative and insurance claims databases, and registries – to evaluate possible safety issues quickly and securely. The Sentinel Initiative will cover 100 million people in the U.S. It is also anticipated that Sentinel will facilitate the development of active surveillance methodologies related to signal detection, strengthening, and validation.