August 23, 2021

Aaron Siri
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Re: Citizen Petition (Docket No. FDA-2021-P-0529)

Dear Mr. Siri,

This letter responds to the citizen petition ("CP") dated May 28, 2021 and the petition for stay of action ("PSA") dated July 6, 2021 that you submitted to the Food and Drug Administration (FDA, the Agency, we) on behalf of the Informed Consent Action Network (ICAN) (Petitioner) regarding data to support any approval of a vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (the Petitions).[1]

In the CP, Petitioner requests that FDA require that sponsors produce the following data before "approving any vaccine for COVID-19:"

1. "Documentation of adverse events and reactions for at least twenty-four months for adults, thirty-six months for children and sixty months for infants and toddlers, or such longer duration as appropriate, and in no event ending prior to the subject reaching eight years of age";
2. "Data demonstrating that safety risks do not outweigh potential benefits for any age for which the vaccine is approved";
3. "Data reflecting that the vaccine does not cause DNA integration and germline transmission";
4. "Data on the safety and efficacy of the vaccine in individuals who currently have or have had a SARS-CoV-2 infection";
5. "Results of reproductive testing including proper immunological studies looking at potential reactivity of the vaccinated against the Syncytin 1 and 2 proteins";
6. "PCR tests used to qualify an event of COVID-19 for a trials' endpoint use a maximum of 28 amplification cycles"; and
7. "Accurate data reflecting actual risk reduction and number needed to vaccinate to

[1] FDA has also received the petitions that you have submitted on behalf of ICAN regarding clinical trials of vaccines to prevent COVID-19 in the following dockets: FDA-2020-P-1601, FDA-2020-P-1768, FDA-2020-P-1769, FDA-2020-P-1770, and FDA-2020-P-2180. FDA either has responded or is responding separately to those petitions.

prevent one case of COVID-19."

In the PSA, Petitioner requests FDA to "stay approval of any COVID-19 vaccine until the sponsor produces" the same data that the Petitioner requests in the CP.

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

I. Background

There is currently a pandemic of respiratory disease, Coronavirus Disease 2019 (COVID-19), caused by a novel coronavirus, SARS-CoV-2. The COVID-19 pandemic presents an extraordinary challenge to global health. On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19.[2] On February 4, 2020, pursuant to section 564 of the FD&C Act, 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.[3] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic ("COVID-19 EUA Declaration"), pursuant to section 564(b)(1) of the FD&C Act.[4] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[5]

Commercial vaccine manufacturers and other entities are developing COVID-19 vaccine candidates, and clinical studies of these vaccines are underway and/or have been completed. Between December 11, 2020 and February 27, 2021, FDA issued emergency use authorizations for three vaccines to prevent COVID-19, including vaccines sponsored by Pfizer Inc. (Pfizer), ModernaTX, Inc. (Moderna), and Janssen Biotech, Inc, (Janssen) a pharmaceutical company of Johnson & Johnson. FDA received a Biologics License Application (BLA) for the BioNTech COVID-19 vaccine, BNT162b2, intended to prevent COVID-19 in individuals 16 years of age and older. As announced by FDA on August 23, 2021, the Agency is issuing a biologics license for this COVID-19 Vaccine (COVID-19 Vaccine, mRNA; Comirnaty) to BioNTech Manufacturing GmbH.[6,7]

II. Vaccines that Are FDA-Licensed Meet Relevant Statutory Requirements

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[2] Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists (Originally issued on Jan. 31, 2020, and subsequently renewed), https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[3] HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.

[4] HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

[5] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak, issued March 13, 2020, https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.

[6] BioNTech Manufacturing GmbH is the biologics license holder for this vaccine, which is manufactured by Pfizer Inc. for BioNTech Manufacturing GmbH (hereinafter "BioNTech").

[7] The basis for FDA's licensure decision is set forth in FDA's Summary Basis for Regulatory Action for the BioNTech application. This memorandum will be posted on fda.gov. We incorporate by reference the SBRA for the BLA.

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.[8,9] 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."[10] 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 BLA for 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.[11]

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.[12] 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."[13] Therefore, the manufacturers of vaccines that have been licensed in the United States have necessarily demonstrated the safety of the vaccines within the meaning of the applicable statutory and regulatory provisions before the vaccines were licensed and allowed to be marketed.

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, 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 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

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[8] 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.
[9] Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[10] 42 U.S.C. § 262(a)(2)(C)(i)(I).
[11] 21 CFR § 601.2(a).
[12] FDA, Vaccines, last updated January 2021, https://www.fda.gov/vaccines-blood-biologics/vaccines.
[13] 21 CFR § 601.2(d) (emphasis added).

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

Section 564 of the Food Drug & 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.[14] On the basis of such determination, on March 27, 2020, the Secretary 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)).[15]

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.

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 demonstrated clear and compelling safety and efficacy in a large, well-designed Phase 3 clinical trial. In the guidance document Emergency Use Authorization for Vaccines to Prevent COVID-19 (October 2020 Guidance), FDA has provided recommendations that describe key information that would

[14] HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.
[15] HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

support issuance of an EUA for a vaccine to prevent COVID-19.[16] 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.[17] FDA has also stated, in this 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.[18]

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

In a Phase 3 study of a COVID-19 vaccine, the efficacy of the investigational vaccine to prevent disease will be assessed by comparing the number of cases of disease in each study group. For Phase 3 trials, FDA has recommended to manufacturers in guidance that the vaccine should be at least 50% more effective than the comparator, and that the outcome be reliable enough so that it is not likely to have happened by chance.[19] 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.

Investigational COVID-19 vaccines continue to be studied. 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. 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.[20] Furthermore, robust safety monitoring will be conducted after a vaccine is made available. The monitoring systems include the Vaccine Adverse Event Reporting System (VAERS), FDA's Biologics Effectiveness and Safety (BEST) System, and the Centers for Disease Control and Prevention's (CDC) Vaccine Safety Datalink. In addition, 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

[16] Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry, October 2020, (October 2020 Guidance) https://www.fda.gov/media/142749/download.
[17] Id. at 3.
[18] Id. at 4.
[19] Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry, June 2020, (June 2020 Guidance), https://www.fda.gov/media/139638/download.
[20] October 2020 Guidance at 10-11.

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.

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

III. Discussion

The CP pertains to the data to be gathered, including during clinical investigations, to support the licensure of a COVID-19 vaccine. FDA's investigational new drug process applies to the development of new drugs and biological products, including vaccines.[21]

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[22]) 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 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 investigational new drug application (IND) to FDA.[23] The IND describes the proposed clinical study in detail and, among other things, helps protect the safety and rights of human subjects.[24] 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),[25] and to adhere to the investigational new drug regulations.

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

[22] 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 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.

[23] See 21 CFR § 312.20(a).

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

[25] 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.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials, unless FDA informs the sponsor that the trial may begin earlier. During this time, FDA reviews the IND. FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and Phase 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.[26]

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.[27]

B. The Citizen Petition

In the CP, Petitioner requests that, before FDA approves any vaccine for the prevention of COVID-19, the agency require certain data be submitted to the agency. Because much of the relevant data is the kind that would be gathered during clinical trials, we interpret the CP as asking that FDA require the sponsors to make the requested changes to their investigations.[28] 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.

Below, we discuss the requested data submissions.[29]

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[26] 21 CFR § 312.22(a).

[27] 21 CFR § 312.42(a).

[28] To the extent 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.

[29] Petitioner's principal arguments in support of the requested actions are premised on the importance of 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. We do not agree that Petitioner has identified a need for FDA to take the requested action. We note that one of the grounds given for Petitioner's requests is that "once the FDA approves a COVID-19 vaccine, states are expected to make this product mandatory, as numerous employers, universities, and schools already have." CP at 3. Concerns about potential third-party vaccine requirements are better directed to those third parties. 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 the agency approves meets all relevant statutory requirements.

1. Adverse Event Documentation

Petitioner asks FDA to require the following information as a condition for approval of a COVID-19 vaccine:

> Documentation of adverse events and reactions for *at least* twenty-four months for adults, thirty-six months for children and sixty months for infants and toddlers, or such longer duration as appropriate, and in no event ending prior to the subject reaching eight years of age.

CP at 2.

FDA agrees that safety monitoring is a critical feature of the vaccine development process, and FDA will not 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 adopt a per se requirement that that the agency will not license a COVID-19 vaccine without the adverse event monitoring specified by the Petitioner.

FDA addressed the topic of safety monitoring 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."[30] 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).[31]

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.

FDA generally expects 6 months of safety follow-up for serious and other medically attended adverse events in a sufficient number of clinical trial participants,[32] but this is not a hard-and-fast rule. The specific vaccine being evaluated, whether longer safety monitoring may be warranted, and the nature of the clinical design, all influence the follow-up period. What the Petition requests is a one-size-fits-all approach to the duration for monitoring safety, with the approach dictating relatively long safety follow-up periods (longer than the safety follow-up period that was used to support the license application for the BioNTech COVID-19 Vaccine; (Comirnaty; COVID-19 Vaccine, mRNA)). Petitioner has not provided adequate scientific evidence to justify the need for the requested across-the-board approach regarding the duration of safety follow-up.

The Petition states that the reason for the requested timeframes is to "provide an opportunity to capture adverse and non-specific health issues that any COVID-19 vaccine may cause before it is approved." CP at

[30] June 2020 Guidance at 15.
[31] Id.
[32] For example, see the June 2020 Guidance at 15.

4. However, the Petition does not explain why *these* timeframes are needed, and why they are *uniformly* needed to support licensure for all COVID-19 vaccines. Petitioner quotes from an article that in turn quotes another article stating, "An approval based on six months of data would represent one of the fastest for a novel vaccine in FDA history. Among the six 'first in disease' vaccines approved by the FDA since 2006, pre-licensure pivotal trials were a median of 23 months in duration, according to a recent analysis."[33] CP at 5. But pointing to an apparent median time period for the duration of a particular trial is not the same as demonstrating scientific justification for a specific duration of safety monitoring. There are many reasons why it may be appropriate to license some vaccines based on clinical trial(s) of shorter duration, and some on clinical trial(s) of longer duration. For example, if a clinical trial enrolls subjects rapidly and the primary endpoint is cases of a disease such as COVID-19 which has a high incidence, cases may accumulate quickly and may allow FDA to assess the benefit-risk profile of the vaccine based on a shorter clinical trial duration. By contrast, if a clinical trial enrolls subjects more slowly and assesses a disease with lower incidence, more time may be needed to accumulate a database that allows statistically meaningful comparisons to be drawn between the vaccine and control groups. FDA's benefit-risk analysis may reasonably take into account the historical experience with vaccines, and the fact that most adverse events that are plausibly linked to vaccination occur within two months of vaccination.[34] Furthermore, vaccine trials involve different types of endpoints, with some trials focusing on surrogate endpoints and some focusing on disease endpoints. All of these features impact the type and duration of data needed to evaluate the risks and benefits of a vaccine. Petitioner fails to account for these nuances.

Another argument Petitioner makes in support of the requested timeframes is what Petitioner describes as an inadequate post-market review system. *See* CP at 5-11. The safety surveillance system that FDA has implemented is working, as evidenced by its ability to detect certain risks associated with each of the authorized COVID-19 vaccines, and FDA has used data from this system to require companies to update fact sheets for vaccine recipients and vaccine providers as appropriate. Moreover, Petitioner fails to explain how the features of a post-market review system justify the specific timeframes requested for clinical trials.[35]

Finally, Petitioner points to what Petitioner characterizes as the clinical trial periods that have been used to support certain other non-vaccine products.[36] But these comparisons are unavailing. Furthermore, as FDA has explained in responses to previous citizen petitions submitted by Petitioner,[37] Petitioner is invoking an

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[33] Doshi, P., Covid-19 vaccines: In the rush for regulatory approval, do we need more data?, BMJ, 373:n1244 (2021), https://www.bmj.com/content/373/bmj.n1244 (citing Kesselheim, AS, JJ Darrow, M Kulldorff, Et al., An Overview of Vaccine Development, Approval, And Regulation, With Implications For COVID-19, Health Affairs, 40:25-32 (2021), https://doi.org/10.1377/hlthaff.2020.01620).

[34] Table VI. National Vaccine Injury Compensation Program. Rockville, MD: Health Resources and Services Administration, 2017, https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf.

[35] As another argument in support of the requested timeframes, Petitioner points to asserted difficulties with the vaccine injury compensation system, stating that "when parents assert that an approved vaccine injured their child, the FDA and CDC regularly deny these assertions by stating that no cause and effect has been established between the vaccination and the alleged injury." CP at 3. Petitioner seems to argue that longer duration trials would allow persons to demonstrate causation in the context of submitting claims for the National Vaccine Injury Compensation Program. But Petitioner has not demonstrated why longer duration trials are necessary to fix asserted problems with the vaccine injury compensation program. Moreover, asserted problems with that program are not properly addressed to FDA, because FDA does not administer and is not responsible for the program.

[36] For example, Petitioner points to clinical trials for Enbrel, Lipitor, and Botox, as well as a description on FDA's website regarding the general drug development process. *See* CP at 10 (citing, for example, https://www.fda.gov/patients/drug-development-process/step-3-clinical-research and https://www.fda.gov/media/102332/download). *Note* that this response does not signal FDA's agreement with how Petitioner has characterized the underlying clinical trial periods supporting the approval of these drugs.

[37] See, e.g., Docket No. FDA-2020-P-2096-0009 at 15; Docket No. FDA-2020-P-1601-0069 at 20.

apples-to-oranges comparison. Many drug products are taken chronically over an individual's lifetime, but that is not the same for many vaccine products. It is not scientifically appropriate to indiscriminately extrapolate approaches to drug development to vaccine development. Therefore, the supposed precedent that Petitioner cites for the requested follow-up periods does not support the action requested.

For the reasons described above, Petitioner has not provided scientific justification for the request that FDA require certain timeframes for clinical trial administration as a condition of licensure. We therefore deny Petitioner's request.

2. Benefits and Risks

As a condition for approval of a COVID-19 vaccine, Petitioner asks FDA to require "[d]ata demonstrating that safety risks do not outweigh potential benefits for any age for which the vaccine is approved." CP at 2. Petitioner further states that existing information "makes clear that the risks of death even after contracting SARS-CoV-2 are extremely low,[38] especially for most age groups younger than 65 years old," and that "[t]he chances of younger individuals contracting the virus and experiencing anything other than mild disease is also incredibly rare." CP at 12. Therefore, according to the Petition, "the benefit/risk analysis should differ for these different groups" and "FDA must demand data from the manufacturers proving that the potential benefit of any vaccine outweighs the minimal risk to most age groups of COVID-19." CP at 12.

Under § 601.2(a), FDA may approve a manufacturer's application for a biologics license only after the manufacturer submits an application accompanied by, among other things, "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency." The BLA must provide the multidisciplinary FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc.) with the Chemistry, Manufacturing, and Controls (CMC)[39] 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]."[40]

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 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.

As the above discussion makes clear, FDA agrees with Petitioner that vaccines should be licensed only upon a showing of a positive benefit-risk profile. The benefit-risk assessment may be informed by the body of evidence about the vaccine's safety and effectiveness submitted by an applicant in the BLA, as well as the severity of the target disease. Thus, in approving or authorizing a vaccine for use in a particular population (such as children), FDA may take into account the severity of the disease in that population as well as the benefits of the vaccine.

However, to the extent that the Petition suggests that FDA should require more data from sponsors regarding the benefits vis-à-vis what Petitioner describes as "minimal risk" of COVID-19, FDA disagrees that the agency should require any particular quantum of data based on the requests in this Petition.

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[38] Despite Petitioner's assertion, we note there have been 600,000 deaths in the United States attributed to COVID-19. See https://www.cdc.gov/nchs/covid19/mortality-overview.htm.

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

[40] 21 CFR § 601.4(a).

Petitioner has not demonstrated any scientific failings with respect to FDA's analysis of benefits and risks of COVID-19 vaccines.

3. Germline Transmission

Petitioner requests that, before FDA licenses any COVID-19 vaccine, the agency require "[d]ata reflecting that the vaccine does not cause DNA integration and germline transmission." CP at 2. Petitioner further states that "[i]t is imperative that the manufacturers are required to submit data to show that viral integration into human DNA is not happening and cannot happen with the use of their COVID-19 vaccine" and that "male participants in clinical trials can and should be monitored." CP at 13. Referring to a guidance document produced by the European Medicines Agency (EMA),[41] Petitioner states that "according to the European Medicines Agency, viral or non-viral vectors may also be associated with a risk of vertical germline transmission of vector DNA." CP at 13.

While there may be some medical products that should be assessed for germline transmission, not all medical products require such investigation. Where the characteristics of the product or other factors are associated with the risk of germline transmission, data collection of the sort recommended by Petitioner may be justified. But where the properties of the product are *not* associated with such risk, such testing may be scientifically unnecessary.

The 2006 EMA Guideline lays out general considerations for non-clinical testing for germline transmission of gene transfer vectors. It notes that a decision to assess potential germline transmission should be approached on a case-by-case basis and take into consideration the vector, dose, route of administration, and proposed clinical indication.[42] With respect to the vector, the Guideline states that assessment of risk should be based on its biodistribution profile, vector replication, and integration ability.[43] In addition, a Considerations document issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) addressing inadvertent germline integration of gene therapy vectors notes, with respect to non-clinical testing, that

> [i]f the vector is not detected in gonadal tissue, then further germline integration studies might not be warranted. If the vector is present in the gonads, animals should be studied to assess whether the level of vector sequence falls below the assay's limit of detection at later time points (i.e., transient detection). A persistent detection of vector sequences in the gonads might warrant elucidation of whether germline cells are transduced.[44]

This ICH Considerations document further states: "If, based on the animal biodistribution studies, the gene therapy vector is found to be transiently detected in the gonads, assaying patient semen for presence of vector might be considered."[45]

Petitioner's request applies, specifically, to FDA's review of BLA submissions for COVID-19 vaccines. There are three vaccines that FDA has authorized for emergency use. One of those vaccines, the Janssen COVID-19 Vaccine, is composed of a recombinant adenovirus type 26 (Ad26) vector, constructed to

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[41] European Medicines Agency, Committee For Medicinal Products For Human Use, Guideline On Non-Clinical Testing For Inadvertent Germline Transmission Of Gene Transfer Vectors, (2006), https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-testing-inadvertent-germline-transmission-gene-transfer-vectors_en.pdf (2006 EMA Guideline).
[42] Id. at 5.
[43] Id.
[44] International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use, General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (2006) at 2, https://admin.ich.org/sites/default/files/2019-04/ICH_Considerations_General_Principles_Risk_of_IGI_GT_Vectors.pdf.
[45] Id. at 3.

contain genetic information encoding the spike (S) protein of SARS-CoV-2.[46] For this vector, the E1 region of the adenoviral genome, which encodes proteins required for virus replication, is deleted, rendering the vector replication-incompetent.[47,48] In addition, the Ad26 vector, as an adenoviral vector, is classified as a non-integrating vector, in that any integration into the host genome, if it occurs at all, occurs at low frequency.[49] These characteristics of the vector used in the Janssen COVID-19 Vaccine are not associated with a risk of vertical germline transmission of vector DNA that would warrant testing for germline transmission. Furthermore, Petitioner has not provided, and we are not aware of, data suggesting distribution of this vector to the gonads.[50] For these reasons, FDA does not consider that this vaccine poses a risk of vertical germline transmission of vector DNA. Therefore, based on the information in the Petition and other currently available information, Petitioner has not demonstrated a scientific need for FDA to require Janssen to submit data to the agency regarding germline transmission studies to support any licensure request.

The other COVID-19 vaccines that FDA has authorized for emergency use are the Moderna and Pfizer-BioNTech vaccines. Both contain messenger RNA (mRNA), which is genetic material. The vaccines contain a piece of mRNA that instructs cells in the body to make the distinctive "spike" protein of the SARS-CoV-2 virus. When a person receives this vaccine, their body produces copies of the spike protein, which does not cause disease, but triggers the immune system to learn to react defensively, producing an immune response against SARS-CoV-2. After vaccination, the body breaks down the mRNA within a matter of hours. Once the mRNA is degraded, no more antigen can be synthesized.[51] These characteristics do not suggest a risk of vertical germline transmission of vaccine material. Indeed, Petitioner has not provided, and we are not aware of, data suggesting distribution of this vector to the gonads.[52] For these reasons, based on the information in the Petition and other currently available information, Petitioner has not demonstrated a need for FDA to require these sponsors to submit the requested data because Petitioner has not demonstrated that the Moderna and Pfizer-BioNTech vaccines present a risk of vertical germline transmission of vaccine material.

For the above reasons, we do not believe Petitioner has demonstrated a scientific justification for FDA to

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[46] A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older; ENSEMBLE; Protocol VAC31518COV3001; Phase 3; AMENDMENT 3; VAC31518 (JNJ-78436735), dated December 14, 2020 (Janssen Ad26.COV2.S Protocol), https://www.jnj.com/coronavirus/ensemble-1-study-protocol at 10.

[47] Janssen Ad26.COV2.S Protocol at 38.

[48] Petitioner seems to imply that adenovirus vectors are not in fact replication incompetent. Petitioner states that "'studies have shown that replication-incompetent adenoviral vectors randomly integrate into host chromosomes at frequencies of 0.001- 1% of infected cells.'" CP at 12 (quoting Mitani, K., S Kubo, Adenovirus as an integrating vector, 2(2):135-44, 2002, https://pubmed.ncbi.nlm.nih.gov/12109211/). But that publication does not provide a scientific basis for germline testing of the Janssen COVID-19 vaccine. The publication does not assess vaccines at all, but rather assesses strategies for successful gene therapy therapeutics and describes the impact of deleting the E1 region as impacting replication.

[49] 2006 EMA Guideline at 4.

[50] Indeed, the Petition itself "concedes that it has not, as it is not able to, provide data suggesting distribution of the vector within viral vector COVID-19 vaccines to the gonads." CP at 13.

[51] Petitioner seems to dispute these characteristics, asserting that "[a]nother study indicates that segments of SARS-CoV-2 viral RNA can become integrated into human genomic DNA and that this newly acquired viral sequence is not silent, meaning that these genetically modified regions of genomic DNA are transcriptionally active (DNA is being converted back into RNA)." CP at 13. But the source article that Petitioner cites does not appear to exist. The source article that Petitioner cites is: https://www.biorxiv.org/content/%E2%80%8Cbiorxiv/%E2%80%8Cearly/%E2%80%8C2020/12/13/2020.12.12.422516.full.pdf . However, as noted in the link, this is a preprint, has not been formally peer reviewed, and "should not be reported as conclusive." Id; https://www.biorxiv.org/content/10.1101/2020.12.12.422516v1. Furthermore, the article does not address reverse transcription of the vaccine mRNA.

[52] As above, we note that the Petition itself "concedes that it has not, as it is not able to, provide data suggesting distribution of the vector within viral vector COVID-19 vaccines to the gonads." CP at 13.

require "[d]ata reflecting that the vaccine does not cause DNA integration and germline transmission" as a condition of licensure of the COVID-19 vaccines currently used in the United States.

4. Data regarding individuals who currently have or have had a SARS-CoV-2 infection

Petitioner requests that, prior to any licensure, FDA require "[d]ata on the safety and efficacy of the vaccine in individuals who currently have or have had a SARS-CoV-2 infection." CP at 2. Although Petitioner asks that FDA require efficacy data for this population, Petitioner's arguments in favor of this request all relate to safety. Below, we address each of these arguments:[53]

a. Petitioner's assertion: "Some medical professionals have opined that vaccinating individuals infected with SARS-CoV-2 is potentially harmful." CP at 14. As support for this statement, Petitioner identifies an online blog post written by a medical doctor on an online open platform website.[54] The blog post includes an email apparently written by the author of the blog post to FDA officials stating that "it is an almost certain immunological prognostication that if viral antigens are present in the tissues, any tissues, of subjects who undergo vaccination, the antigen specific immune response triggered by the vaccine will target those tissues and cause inflammation and damage beyond the local anatomic site of vaccine placement." The blog post also states that "when viral antigens are present in the vascular endothelium or other layers of the blood vessel, and especially in elderly and frail with cardiovascular disease, the antigen specific immune response incited by the vaccine is almost certain to do damage to the vascular endothelium."

   FDA response: The blog post does not contain any data or citations to the medical literature supporting the "almost certain" risk. We therefore conclude that the blog post does not provide a data-backed basis for the requested action. We further note that the blog post does not provide any scientific basis for explaining why the immune response to the viral antigens attributed to the vaccine is more dangerous than the immune response to the viral antigens produced as a result of SARS-CoV-2 infection.

   Petitioner's assertion: "Numerous medical professionals have opined that if an individual who is vaccinated has viral antigens present in any tissues in the body, the antigen specific immune response triggered by the vaccine will target those

[53] We note that history of infection prior to vaccination is not usually known in adverse event reports (either because it wasn't reported, or because it could have been asymptomatic and the patient never knew they had infection). Likewise, there could be a reporting bias for a reporting system like VAERS, which relies on vaccine recipients, healthcare providers, or others to initiate reports to the system, because individuals who were infected previously might be more likely to report adverse events. However, FDA, together with CDC, has not become aware of data from VAERS to suggest an increased frequency of adverse events in vaccinees who were infected with SARS-CoV-2 prior to vaccination. FDA and CDC Medical Officers conduct on-going review of certain, serious adverse events of special interest for the COVID vaccines. These reviews often include examination of the narrative and other fields which would contain information about past infection, if provided. Additionally, CDC and the VAERS Program contractor collect follow-up medical records for certain serious reports. Teams of physicians, nurses, and other reviewers abstract key clinical details, including medical history, from these records. The reviewers conducting these on-going surveillance efforts have not identified patterns of adverse events associated with prior infection.

[54] https://noorchashm.medium.com/a-letter-of-warning-to-fda-and-pfizer-on-the-immunological-danger-of-covid -19-vaccination-in-the-7d17d037982d

tissues and will cause inflammation and damage at those locations and well beyond the local site of vaccination." CP at 14.

FDA response: Petitioner does not identify any medical professionals who share this concern, other than the one author of the blog post discussed above. Nor does Petitioner provide any citations to the scientific literature. Therefore, we conclude that this statement does not set forth a factual or scientific basis for the requested action.

b. Petitioner's assertion: "Recent data from the UK reflects that individuals with prior infections have the most intense vaccine-related adverse reactions." CP at 14. As support for this statement, Petitioner cites a publication reporting on the results of an "international, online survey . . . to compare the safety, tolerability and reactogenicity of available COVID-19 vaccines in different recipient groups."[55]

FDA response: While the publication reports that that "our study links prior COVID-19 illness with increased incidence of vaccination side effects," we note that the authors themselves acknowledge potential respondence bias and recall bias as potential limitations to interpreting the results. We also note that, in light of the full body of data that FDA has evaluated since the development of the COVID-19 vaccines, we have not identified any safety signals linked to prior infection that merit requirements for sponsors to submit additional data to FDA on this topic.

c. Petitioner's assertion: "There are some very prominent examples of death and complications from COVID-19 vaccination of the recently infected. These examples include Dr. J. Barton Williams of TN, Mr. Christopher Sarmiento of NM, and Ms. Brandy Parker-McFadden of TN." CP at 14. As support for this statement, Petitioner cites a news article on the website of a Nashville television station that describes the experience of Ms. Parker-McFadden, who reportedly experienced paralysis soon after receiving a second dose of the Pfizer vaccine.[56] Petitioner goes on to assert that "[t]hese people had prior infections and developed serious post-vaccine complications and are only three prominent examples of what is likely a far wider issue."

FDA response: We note that the news article that the Petitioner relies on for support does not include any information about whether the individual featured in the story had prior SARS-CoV-2 infection. We also note that the article itself states that a formal investigation into the cause of the woman's paralysis had not yet occurred at the time of publication. FDA takes all reports of adverse events linked to COVID-19 vaccines seriously, but this information provided by the Petition does not support the action requested because it is not even clear whether the featured individual experienced prior infection and it is similarly not clear from the information provided whether the individual's symptoms were caused by the vaccine. Petitioner also fails to provide any information supporting Petitioner's broad assertion that complications in those who experienced SARS-

[55] https://www.medrxiv.org/content/10.1101/2021.02.26.21252096v1

[56] Davis, A., Nashville woman unable to walk claims Pfizer COVID-19 vaccine is to blame, WKRN.COM (2021), https://www.wkrn.com/news/nashville-woman-unable-to-walk-claims-pfizer-covid-19-vaccine-is-to-blame/

CoV-2 infection and subsequently received a vaccine to prevent COVID-19 is "likely a far wider issue."

5. Reproductive Testing

Prior to licensing any COVID-19 vaccines, Petitioner requests that FDA require sponsors to submit "[r]eproductive testing including proper immunological studies looking at potential reactivity of the vaccinated against the Syncytin 1 and 2 proteins." CP at 2. We address each of Petitioner's assertions to explain why they do not provide a factual or scientific basis for FDA's taking action in response to the Petition:

a. Petitioner's assertion: "Close conformational and functional similarity of the SARS CoV-2 spike protein to the Syncytins has been observed." CP at 15.

   FDA response: Petitioner does not provide any citations or other scientific information to support this assertion.

b. Petitioner's assertion: "This is supported by the observations that there is impaired spermatogenesis in some during and following the natural COVID-19 infection as well as the localization of spike protein to testes." CP at 15. As support for this statement, Petitioner provides a website link that does not work.[57]

   FDA response: Because Petitioner did not provide enough information for FDA to locate the source of this assertion, FDA cannot evaluate the supposed source of this information. However, we note that the conclusion that Petitioner appears to draw from the missing publication relates only to "natural COVID-19 infection," and not any vaccines.

c. Petitioner's assertion: "Additionally, a placental pathology has been observed in some COVID-infected women reminiscent of pre-eclampsia, and Syncytin 1 knockout mice exhibit similar placental pathology coupled with the inability to carry to full term." CP at 15. As support for this statement, Petitioner refers to a publication from 2017.[58]

   FDA response: The scientific evidence that Petitioner identifies here is a study that was published two years before the first reported case of SARS-CoV-2. The publication contains no information specific to SARS-CoV-2 and the vaccines aimed at preventing COVID-19.

d. Petitioner's assertion: "There have also been noted a significant number of miscarriages that have been reported in the VAERS reporting system following vaccination for COVID-19 to date. These all support the premise that the COVID-19 vaccines which direct the body to make the SARS-CoV-2 spike protein may be causing reproductive harm either directly through spike protein or through a cross-reaction mechanism with the endogenous Syncytins." CP at 15.

   FDA response: While VAERS is a critical part of FDA's post-market safety monitoring system for vaccines, adverse events reported to VAERS are not

[57] *See* https://beta.documentcloud.org/documents/20404854-histopathology-and-ultrastructural-findings-of-fatal-co%E2%80%8Cvid%E2%80%8C-%E2%80%8C19-infections-on-testis. FDA checked this website link on July 27, 2021.
[58] Shin Qiao et al., Inducible knockout of Syncytin-A gene leads to extensive placental vascular deficiency, implications for preeclampsia. Clin Chim Acta Nov. 474:137-146 (2017).

adverse events confirmed to be associated with vaccination. Some reported adverse events may be caused by vaccination, but others are not and may have occurred as a result of chance. Miscarriages are generally expected to occur in a certain number of pregnancies, in the United States general population the estimated background risk of miscarriage in clinically recognized pregnancies is 15 to 20 percent.[59] There is no evidence at this time indicating that the number of reports of miscarriage to VAERS is higher than would normally be expected from this background rate.[60]

e. Petitioner's assertion: "This issue of a potential for cross-reaction to the Syncytins through the use of COVID-19 vaccines was raised by scientists over a year ago." CP at 15. As support for this assertion, Petitioner provides a website link that does not work.[61]

FDA response: Because Petitioner did not provide enough information for FDA to locate the source of this assertion, FDA cannot evaluate the supposed source of this information. However, we note that our assessment of the science is that there is not a credible basis for the conclusion that Petitioner appears to draw from the missing publication—that the immune response to the SARS-CoV-2 spike protein cross-reacts with placental protein syncytin 1 and damages the placenta. Given the lack of similarity between the SARS-CoV-2 spike protein and the syncytin 1 protein, it is biologically implausible that an immune response to the spike protein would target the syncytin 1 protein.

6. PCR Tests and Amplification Cycles

Petitioner requests that "PCR tests used to qualify an event of COVID-19 for a trials' endpoint use a maximum of 28 amplification cycles." CP at 2. The Petitioner states that "[t]here are serious issues associated with the trials' use of the PCR test as the linchpin in determining whether a participant has COVID-19 disease," and that the trials "must account" for the fact that PCR tests have "an incredibly high rate of false positives." CP at 15-16. With respect to the amplification cycle request, Petitioner states that the "number of PCR cycles it takes to amplify a sample containing viral remains to the point where they can be detected is called its cycle threshold" and that such a threshold "must be set at a reasonable number." CP at 16.

This is not a new request from Petitioner. In one of Petitioner's previous citizen petitions to the agency regarding COVID-19 vaccines, Petitioner requested that FDA require PCR tests in vaccine clinical trials to use a maximum of 24 amplification cycles.[62] We incorporate our response to that request in full,[63] and we deny Petitioner's request here for the same reasons as stated in the earlier response. In short, such a requirement, in and of itself, is arbitrary and is unrelated to a determination of the infected status of the tested individual. Different amplification cycle cut-offs may be justified for different PCR tests. The

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[59] See e.g., Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry Draft Guidance, July 2020, rev. 1, at 8.

[60] *See, e.g.,* Shimabukuro et al., Preliminary Findings of MRNA Covid-19 Vaccine Safety in Pregnant Persons, New England Journal of Medicine (2021) (concluding that "[p]reliminary findings did not show obvious safety signals among pregnant persons who received MRNA Covid-19 vaccines").

[61] *See* https://dryburgh.com/wp-content/uploads/2020/12/Wodarg_Yeadon_EMA_Petition_Pfizer_Trial_FINAL_%E2%80%8C01%E2%80%8CDEC2020_signed_with_Exhibits_geschwarzt.pdf. FDA attempted to access this website link on July 27, 2021.

[62] *See* Docket No. FDA-2020-P-2180-0001, at 2.

[63] Docket No. FDA-2020-P-2180-0070, at 8-10.

variability across tests is one reason why Petitioner's request would not be justified. Another reason why Petitioner's request is not justified is that the number of amplification cycles used is just one factor that affects the reliability of a PCR result.[64]

With this latest Petition, Petitioner asserts that new "CDC guidance" for tracking "breakthrough" infections calls for a maximum of 28 cycles, and that "FDA must explain" why CDC has a cutoff that FDA is not imposing for vaccine clinical trials. CP at 19. Unfortunately, the website link that Petitioner provides for the supposed CDC guidance does not work.[65] But we were able to find a CDC document that uses the same quote that Petitioner includes in the Petition ("have an RT-PCR Ct value ≤28").[66] That document contains instructions to state public health labs about reporting breakthrough cases that also states the CDC's interest in sequencing such specimens, and the full excerpt from which Petitioner quotes reads as follows: "For cases with a known RT-PCR cycle threshold (Ct) value, submit only specimens with Ct value ≤28 to CDC for sequencing. (Sequencing is not feasible with higher Ct values.)."[67] Thus, the CDC document does not identify a cycle cutoff for the accuracy reasons underlying Petitioner's request; rather, the CDC states that the cycle cutoff is for the entirely different purposes of facilitating sequencing to assess for variants. Thus, the "CDC guidance" that Petitioner cites as a basis for FDA taking action does not in fact stand for the proposition for which Petitioner cites it. The new "CDC guidance" therefore does not constitute a basis for FDA granting Petitioner's request. For all of the reasons identified in FDA's previous citizen petition response, FDA denies the request for an across-the-board amplification cycle cutoff.

7. Data regarding risk reduction

Petitioner asks that, prior to licensing any COVID-19 vaccine, FDA require "[a]ccurate data reflecting actual risk reduction and number needed to vaccinate to prevent one case of COVID-19." CP at 2. Petitioner states that communicating information in terms of absolute risk is more informative, and that "the data reviewed by the FDA to issue EUAs did not take into account the number needed to vaccinate." CP at 20.

We disagree that Petitioner's request should be a basis for a licensure decision. FDA's authorizing statute provides that FDA "shall" license biological products that are shown to be "safe, pure, and potent."[68] Products can be shown to be safe, pure, and potent even when sponsors have not presented the FDA with data regarding absolute risk reduction and the number needed to vaccinate to prevent one case of disease. Indeed, FDA's regulations on adequate and well-controlled studies (21 CFR 314.126) describe several kinds of controlled trials that may provide evidence of effectiveness. This reflects the fact that evidence can be demonstrated with different types of data, and no single type of data is always required for all

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[64] *See* id., at 9.

[65] https://www.cdc.gov/vaccines/covid-19/downloads/Information-for-laboratories-COVID-vaccine-breakthrough-case%E2%80%8C-investigation.pdf

[66] CDC, COVID-19 Breakthrough Case Investigations and Reporting (April 17, 2021), https://stacks.cdc.gov/view/cdc/105217/cdc_105217_DS1.pdf. We note that the referenced document appears to be a printout of the CDC website on April 17, 2021. The current version of the website notes that CDC has shifted away from monitoring breakthrough cases to focus on "investigating only hospitalized or fatal cases due to any cause" in order to "help maximize the quality of the data collected on cases of greatest clinical and public health importance." CDC, COVID-19 Breakthrough Case Investigations and Reporting, https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html.

[67] The CDC instructions for labs makes sense. In order to get a quality genome sequence of SARS-CoV-2 from a clinical sample, there needs to be a sufficient amount of virus present. If there is too little virus then the sequencing reaction will not produce results of sufficient quality to completely assess the entire genome. Without the entire (or near entire) genome there are limited investigations which can be done. This has nothing to do with a determination of the infectivity status (or any other health status) of the patient from which the sample was taken.

[68] 42 U.S.C. 262(a)(2)(C)(i)(I).

products.[69] FDA will not license any products that fail to meet relevant statutory and regulatory standards, and, at the same time, FDA will not impose requirements that may not be necessary to meet those standards. Accordingly, we deny Petitioner's request.

IV. The Petition for Stay

In the PSA, Petitioner requests FDA to "stay approval of any COVID-19 vaccine until the sponsor produced" the following data:

> 1. "Documentation of adverse events and reactions for *at least* twenty-four months for adults, thirty-six months for children and sixty months for infants and toddlers, or such longer duration as appropriate, and in no event ending prior to the subject reaching eight years of age";
> 2. "Data demonstrating that safety risks do not outweigh potential benefits for any age for which the vaccine is approved";
> 3. "Data reflecting that the vaccine does not cause DNA integration and germline transmission";
> 4. "Data on the safety and efficacy of the vaccine in individuals who currently have or have had a SARS-CoV-2 infection";
> 5. "Results of reproductive testing including proper immunological studies looking at potential reactivity of the vaccinated against the Syncytin 1 and 2 proteins";
> 6. "PCR tests used to qualify an event of COVID-19 for a trials' endpoint use a maximum of 28 amplification cycles"; and
> 7. "Accurate data reflecting actual risk reduction and number needed to vaccinate to prevent one case of COVID-19."

PSA at 2-3.

8. Criteria for Granting an Administrative Stay of Action

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

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

> The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition…The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:
> (1) The petitioner will otherwise suffer irreparable injury.

[69] We note that the FDA document entitled "Communicating Risks and Benefits: An Evidence-Based User Guide" that Petitioner quotes on pages 19-20 of the CP does not address evidence needed to support product approvals. Rather, it contains information about best practices for communicating risk information. *See* https://www.fda.gov/files/about%20fda/published/Communicating-Risk-and-Benefits---An-Evidence-Based-User%27s-Guide-%28Printer-Friendly%29.pdf.

(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.[70]

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

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

a. Petitioner Has Not Demonstrated Irreparable Injury

Petitioner contends that a stay must be granted because Petitioner will suffer irreparable injury. PSA at 3. Specifically, Petitioner argues that "once the FDA approves a COVID-19 vaccine, states are expected to make this product mandatory, as hundreds of employers, universities, and schools already have." PSA at 3. Petitioner also states that "without the FDA assuring proper safety and efficacy trials of the vaccine now, Petitioners will not have the opportunity to object to receiving the vaccine based on deficient clinical trials later." PSA at 3.

Petitioner's claim of injury is too remote. Petitioner asserts that Petitioner will be forced to receive an inadequately vetted vaccine due to vaccination requirements at the State and third-party level. However, the PSA does not seek a stay of any FDA decision that will force any individuals to receive a vaccine (nor has FDA imposed a vaccination requirement). Petitioner seeks only for FDA to require certain data as a condition of licensing a vaccine. However, Petitioner has not demonstrated that FDA's actions will cause States or other entities to issue requirements that will in turn cause Petitioner to be vaccinated against Petitioner's will. First, the policies that Petitioner identifies are not in fact requirements for forced vaccinations. Rather, these are policies that typically place conditions on employment, education, receipt of services, and the like rather than more direct legal requirements. There are numerous regulatory steps between FDA licensure and the possibility, however remote, of any individual being forced to be vaccinated against their will.[71] Furthermore, FDA makes decisions to license vaccines based on whether they have been shown to be safe, pure, and potent—not on whether any third parties may issue policies that condition employment, schooling, etc. on the use of vaccines. The licensure of any COVID-19 vaccine, alone, will not cause the asserted harm.

Thus, Petitioner has not demonstrated that FDA licensure of a vaccine not in accordance with the petition will cause irreparable injury.

[70] 21 CFR § 10.35(e).

[71] Concerns about potential State or employer vaccine requirements should be directed to those entities because FDA does not determine third parties' vaccination policies. Similarly, FDA does not impose federal mandates for the 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 licensed meets all relevant statutory requirements.

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

Petitioner asserts, but does not provide evidence to support the assertion, that "the request demonstrates sound public policy." PSA at 3. The Petitioner's only assertion with respect to sound public policy grounds is that "[p]ublic policy dictates that nothing but the scientific data should justify or motivate FDA approval of a product." PSA at 4.

We do not agree that Petitioner has demonstrated sound public policy grounds supporting a stay. Petitioner suggests that FDA may allow something other than the "scientific data" to justify an FDA approval but provides no evidence for this. The PHS Act dictates that FDA shall approve a biological product that has been shown to be safe, pure, and potent. Petitioner has not shown that the data supporting any particular BLA does not meet this standard. It would constitute *unsound* public policy if FDA refused, despite its statutory mandate, to license a vaccine that has been shown to be safe, pure, and potent only because certain data requested by Petitioner was not provided—especially when Petitioner has not demonstrated that the requested data is necessary (see discussion above). Therefore, we disagree that Petitioner has demonstrated sound public policy grounds supporting the requested stay. We note that if FDA receives a BLA that does not meet the standards for licensure, FDA will not license the product.

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

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

> The public interest also weighs strongly in favor of the requested relief because conducting adequate safety reviews, DNA integration and germline transmission testing, safety testing for the infected and convalesced, reproductive testing, and adequate efficacy assessments (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) not doing so will have the opposite result in that it will create uncertainties regarding the safety of COVID-19 vaccines and all other vaccines. A thorough evaluation of already-existing post-authorization data is critical before licensure.

PSA at 4.

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

In addition, the extraordinary current public health situation further argues against any unnecessary delay in the timely licensure of a COVID-19 vaccine that meets all relevant regulatory requirements. Nor has Petitioner demonstrated that the requested data is necessary (see discussion above). Delaying licensure to require certain data submissions in response to a request that that lacks scientific justification would compromise the public health and public interest in vaccine development. The interests of public health would not be served if a stay interfered with licensure of a COVID-19 vaccine without justification.

9. 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 vaccines are licensed when there is data showing that the relevant standards have been met. It

is not in the public interest or the interest of justice to stay licensure to require certain data submissions in response to a request that that lacks scientific justification.

For the foregoing reasons, the PSA is denied.

V. Conclusion

FDA has considered Petitioner's requests as they relate to the licensure of COVID-19 vaccines. For the reasons given in this letter, FDA denies the requests in the Petitions. Therefore, we deny the Petitions in their entirety.

Sincerely,

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

cc: Dockets Management Staff

Appendix: 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. VAERS is co-administered by 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 US 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.