February 27, 2021

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

Re: Citizen Petition (Docket Number FDA-2020-P-2096)

Dear Mr. Siri,

This letter responds to the citizen petition dated October 16, 2020 that you submitted to the Food and Drug Administration (FDA, the Agency, we) on behalf of the Informed Consent Action Network (ICAN) (Petitioner) relating to the clinical trial of Ad26.COV2.S, a vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (the CP).[1,2]

In the CP, Petitioner requests that the study design for the Phase 3 trial of Ad26.COV2.S be amended to provide that:

> a. any and all adverse events and reactions[] will be documented for the entire duration of the trial;
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> b. such documenting of adverse events and reactions shall last *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 end prior to the subject reaching eight years of age;
>
> c. it uses an adequate sample size, appropriately powered, in order to (i) detect an increase in rare adverse events or any untoward medical occurrence, whether or not considered vaccine related, and (ii) determine that the rate of adverse events from the vaccine will not exceed the rate of adverse events known to occur from SARS-CoV-2 in the group under review[];

[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.
[2] We note that the other sets of petitions that you submitted on behalf of ICAN addressing clinical trials of vaccines to prevent COVID-19 included petitions submitted pursuant to 21 C.F.R. § 10.35 (Petitions for administrative stay of action). We are not aware of any such petition that you have submitted that is specific to the clinical trial of Ad26.COV2.S.

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

e. germline transmission tests are conducted for male participants; and

f. HIV incidence will be "monitored at the end of the study and for an appropriate follow-up period"[] and the trial will "evaluate the levels and distribution of both vector and insert responses in target tissues where HIV acquisition is known to occur."[]

CP at 2.

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

Here is an outline of our response:

I. Background

There is currently a pandemic of respiratory disease, 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 vaccine candidates are underway. On February 4, 2021, Janssen Biotech, Inc. (Janssen) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine, Ad26.COV2.S, intended to prevent COVID-19.[5] As announced by FDA on February 27, 2021, the Agency is granting EUA for the Janssen COVID-19 Vaccine.[6]

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.[7,8] 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."[9] 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.[10]

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

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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] FDA Briefing Document, Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19, Vaccines and Related Biological Products Advisory Committee Meeting, February 26, 2021, at 6 (FDA Janssen COVID-19 Vaccine Briefing Document), https://www.fda.gov/media/146217/download.
[6] FDA EUA Letter of Authorization for the Janssen COVID-19 Vaccine dated February 27, 2021 (Janssen COVID-19 Vaccine EUA Letter of Authorization), https://www.fda.gov/media/146303/download.
[7] 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.
[8] Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[9] 42 U.S.C. § 262(a)(2)(C)(i)(I).
[10] 21 CFR § 601.2(a).

safety, purity, and potency of a vaccine has been demonstrated.[11] 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."[12] Therefore, the manufacturers of vaccines that have been licensed in the United States (U.S.) 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.

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, 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

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.[13] On the basis of such determination,

[11] Vaccines, last updated June 2020, https://www.fda.gov/vaccines-blood-biologics/vaccines.
[12] 21 CFR § 601.2(d) (emphasis added).
[13] 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.

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)).[14]

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 support issuance of an EUA for a vaccine to prevent COVID-19.[15] 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.[16] 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.[17]

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

[14] 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.
[15] Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry, October 2020, https://www.fda.gov/media/142749/download.
[16] Id. at 3.
[17] Id. at 4.

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.[18] During the entire study, subjects will be monitored for safety events. If the evidence from the clinical trial meets the pre-specified criteria for success for efficacy and the safety profile is acceptable, the results from the trial can potentially be submitted to FDA in support of an EUA request.

Several investigational COVID-19 vaccines are now being studied in Phase 2 or Phase 3 trials. Following clinical trials, manufacturers analyze data prior to submitting to FDA a BLA to request approval from FDA to market the vaccine. A BLA for a new vaccine includes information and data regarding the safety, effectiveness, chemistry, manufacturing and controls, and other details regarding the product. The goal timelines for FDA's comprehensive BLA review and evaluation are detailed in the Prescription Drug User Fee Act (PDUFA) goals letter and range from 6-10 months after the application has been filed.[19] 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. This monitoring is done for newly-approved vaccines and will be expanded for the use of COVID-19 vaccines. 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 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.

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

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

[20] October 2020 Guidance at 10.

III. Discussion

The CP pertains to "the study design for the Phase III trial of Ad26.COV2.S" (CP at 2), which is an investigational vaccine to prevent COVID-19. 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 "the study design for the Phase III trial of Ad26.COV2.S…be amended" to include certain design characteristics relating to: the documentation of adverse events; sample size; testing for T-cell reactivity to SARS-CoV-2; germline transmission tests; and human immunodeficiency virus (HIV) incidence monitoring and evaluation of certain target tissues.[28] CP at 2. Because FDA does not itself create or amend drug investigations,[29] we

[26] 21 CFR § 312.22(a).
[27] 21 CFR § 312.42(a).
[28] The Agency notes that Petitioner "incorporates by reference…the Statement of Grounds from its Amended Citizen's Petition, dated July 20, 2020." CP at 3, footnote 7. That July 20, 2020 petition, contained in Docket Number FDA-2020-P-1601, relates, in part, to Phase 2 and Phase 3 trials of COVID-19 vaccines in general. Although it does not address the Ad26.COV2.S clinical trial (the subject of the CP) specifically, we have considered the Statement of Grounds from the July 20, 2020 petition in responding to the CP. We have responded to the July 20, 2020 petition and the related submissions contained in Docket Number FDA-2020-P-1601 separately.
[29] 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.

interpret the CP as asking that FDA require the sponsors to make the requested changes.[30] 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 changes to the study design.[31]

1. Adverse Event Documentation

Petitioner asks FDA to require that the study design for the Phase 3 trial of Ad26.COV2.S document "any and all adverse events and reactions…for the entire duration of the trial." CP at 2. Petitioner specifies that this

> includ[es], but [is] 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.

CP at 2, footnote 3.

Petitioner also requests that "such documenting of adverse events and reactions shall last *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 end prior to the subject reaching eight years of age." CP at 2.

Because the CP refers to adverse event monitoring in the context of a Phase 3 trial, 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 the Ad26.COV2.S vaccine provide the specified adverse event monitoring.

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

[30] 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.

[31] Petitioner's principal arguments in support of the requested actions reiterate 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 grounds given for Petitioner's requests is that "states are expected to make this product mandatory." CP at 3. 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, including Ad26.COV2.S, that is authorized or approved meets all relevant statutory requirements.

different than for other preventive vaccines for infectious diseases."[32] 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).[33]

With respect to the EUA of a COVID-19 vaccine, 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 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).[34]

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.

a. Petitioner's Requests to Document All Adverse Events

Petitioner requests that "any and all adverse events and reactions…be documented." CP at 2. Petitioner specifies that this

[32] June 2020 Guidance at 15.
[33] Id.
[34] October 2020 Guidance at 10.

> [i]nclud[es], but [is] 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.

CP at 2, footnote 3.

In support of this request, Petitioner identifies what Petitioner characterizes as deficiencies with the safety follow-up procedures in the Ad26.COV2.S protocol. Petitioner asserts that

> [t]he current study design for Ad26.COV2.S Vaccine provides that "adverse events"… should be captured for only 28 days post-vaccination in only a subset of the participants (the "safety subset"). The safety subset is made up of only 3,000 participants receiving the vaccine and 3,000 receiving the placebo – this is a mere 10% of all participants in the trial. For 90% of trial participants, [adverse events] will not be tracked. Medically attended adverse events…are only captured for 6 months post-vaccination (unless the [medically attended adverse event] leads to discontinuation of the study, when it would then be tracked during the entire study), while "serious adverse events"…are tracked during the entire study. Thus, for any participant not a part of the safety subset, [adverse events] will not be tracked at all unless they are medically attended (and within 6 months of vaccination) or "serious"

(emphasis omitted). CP at 4. Petitioner also asserts that "[g]iven that 'serious adverse events' are already being captured for the duration of the study, it appears foolhardy to not also capture *all* adverse events." CP at 5.

Because Petitioner takes issue with the safety follow-up procedures in the Ad26.COV2.S clinical trial, it is helpful to note that Petitioner's description of the procedures appears to be based on a summary of clinical trial information posted on clinicaltrials.gov. CP at 2, footnote 2. Separate from the information on clinicaltrials.gov, Janssen has made publicly available the protocol for Ad26.COV2.S.[35] The safety follow-up for the clinical trial, as described in the Janssen Ad26.COV2.S Protocol, includes, for each participant, monitoring and recording of: all serious adverse events for up to two years after vaccination; all adverse events leading to study discontinuation until completion of the last study-related procedure; and medically attended adverse events (including new onset of chronic diseases) until six months after vaccination.[36] In addition, the design for the Ad26.COV2.S clinical trial calls for a Safety Subset, consisting of approximately 6,000 of the study participants (approximately 3,000 from the active group and 3,000 from the placebo group), for which additional safety information is collected.[37] For participants in the Safety Subset, solicited local and systemic adverse events, collected through an e-Diary, are monitored and recorded from the time of vaccination until 7 days post-

[35] 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.
[36] Id. at 102-103.
[37] Id. at 22.

vaccination, and all other unsolicited adverse events, whether serious or non-serious, are monitored and recorded from the time of vaccination until 28 days post-vaccination.[38]

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.[39] 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.[40] 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.[41] 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.[42]

Comprehensive safety data, including essentially all adverse events, are collected in the early stages of drug development.[43] 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 this value and would require extensive resource utilization, while providing no important new information.[44] In addition, FDA has stated that a plan for selective safety data collection could involve collecting safety data about non-serious adverse events from a sample of the study population.[45] Use of a Safety Subset in late-stage clinical trials to gather additional information on adverse events that are not serious or medically-attended is thus consistent with FDA's existing policies regarding safety data collection. We also note that, in the case of the Ad26.COV2.S clinical trial, the number of participants from the active group contained in the

[38] Id. at 103.
[39] Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations; Guidance for Industry, February 2016 (Safety Data in Late-Stage Premarket and Postapproval Clinical Investigations Guidance), at 6, https://www.fda.gov/media/82664/download.
[40] Id. at 7.
[41] See Establishment and Operation of Clinical Trial Data Monitoring Committees; Guidance for Clinical Trial Sponsors, March 2006, at 1, https://www.fda.gov/media/75398/download.
[42] June 2020 Guidance at 15.
[43] Safety Data in Late-Stage Premarket and Postapproval Clinical Investigations Guidance at 2.
[44] Id.
[45] Id. at 6.

Safety Subset (approximately 3,000) is as large as the pre-licensure safety database that FDA typically recommends for preventive vaccines for infectious diseases.[46]

Documenting "any and all adverse events and reactions," as Petitioner requests, would likely result in the collection of information that would not necessarily be of value in assessing the safety of the Ad26.COV2.S vaccine. 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 extraneous 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.[47]

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.

FDA has considered the types of adverse events that have been documented during the Ad26.COV2.S vaccine clinical trial, and has determined that this aspect of the trial design provides the Agency with useful information that is sufficient to permit FDA to determine that the relevant statutory criteria for an EUA for this product have been met. We do not believe that Petitioner has explained why a requirement that the sponsor collect "any and all" adverse events and reactions during the late-stage vaccine trial would be necessary, and we do not believe that Petitioner's requests should be criteria for an EUA. For the reasons described above, we believe that requiring the indiscriminate collection of data could be problematic. We therefore deny Petitioner's request.

b. 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.[48] As described in the June 2020 Guidance, FDA expects that all COVID-19 clinical study participants be monitored for the occurrence of serious and other

[46] "The 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." June 2020 Guidance at 15.
[47] Safety Data in Late-Stage Premarket and Postapproval Clinical Investigations Guidance at 3.
[48] Premarketing Risk Assessment; Guidance for Industry, March 2005 at 9; https://www.fda.gov/media/71650/download.

medically attended adverse events for at least 6 months after completion of all study vaccinations.

In order to issue an EUA, 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.[49] FDA's October 2020 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 post-vaccination period.[50] Adverse events considered plausibly linked to vaccination generally start within 6 weeks after vaccine receipt.[51] 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 vaccines 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. 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 submitting an EUA request.

Regarding the request in the CP that the Ad26.COV2.S clinical trial track adverse events for at least 24 months for adults, for the reasons described above, we do not believe that such a follow-up is needed to support an EUA for this COVID-19 vaccine at this time. Thus, we are issuing an EUA which is supported by analysis of safety data from 43,783 participants enrolled in an ongoing randomized, placebo-controlled study being conducted in South Africa, certain countries in South America, Mexico and the U.S.[52] These participants, 21,895 of whom received the vaccine and 21,888 of whom received saline placebo, were followed for a median duration of eight weeks after vaccination.[53] This follow-up period is justified based on the need for vaccines 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 an EUA. Therefore, we deny the request to require a 24-month follow-up period for adults, and we

[49] October 2020 Guidance at 10.
[50] Id.
[51] Health Resources and Services Administration, Vaccine Injury Table, 2017, https://www.hrsa.gov/sites/default/files/vaccinecompensation/vaccineinjurytable.pdf.
[52] For a more complete description of FDA's safety evaluation, see the Janssen COVID-19 Vaccine Emergency Use Authorization Review Memorandum.
[53] See id.

do not believe this must be a condition of authorization for the Ad26.COV2.S COVID-19 vaccine.

Regarding Petitioner's request that FDA require, at this time, that the Ad26.COV2.S clinical trial track adverse events for 36 months for children 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. Petitioner has not identified scientific support showing that the requested pediatric follow-up periods are necessary for vaccine clinical trials.[54] Petitioner relies on a 2019 publication authored by researchers at 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. CP at 6-7. 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 Petitioner's request that all adverse events be documented for the entire duration of the Ad26.COV2.S COVID-19 vaccine clinical trial, we note that this, too, would collect information of no 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 or losing important information, facilitate patients' participation in clinical studies, and help contain costs by making more-efficient use of clinical study resources.[55]

FDA has considered the periods of time over which the Ad26.COV2.S study collects safety data, and has determined that this aspect of the trial design provides the Agency with useful information that is sufficient to permit FDA to determine that the relevant statutory criteria for an EUA for this product have been met. For these reasons, FDA denies Petitioner's request to require the clinical trial of the Ad26.COV2.S vaccine to document adverse events for the requested duration, and we do not believe this should be a condition of the EUA.

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.[56] FDA's June 2020 Guidance advises that follow-up of study participants for COVID-19 outcomes should

[54] We also note that, for Ad26.COV2.S, Janssen's proposed use under the EUA is for individuals 18 and older and FDA's authorization does not extend to pediatric populations. For more information about the populations covered by the authorization, see the Janssen COVID-19 Vaccine EUA Letter of Authorization.
[55] Safety Data in Late-Stage Premarket and Postapproval Clinical Investigations Guidance at 3.
[56] June 2020 Guidance at 16.

continue as long as feasible, ideally at least one to two years.[57] 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 evaluate important identified or potential risks from the clinical development program, such as uncommon or delayed-onset adverse events of special interest.[58]

As will be the case for any COVID-19 vaccine, the Ad26.COV2.S vaccine will be subject to robust safety monitoring after authorization. The Ad26.COV2.S vaccine will be subject to U.S. government monitoring systems, including VAERS, FDA's BEST System, and CDC's Vaccine Safety Datalink, as described in section II.B. of this response. In addition, as stated in the Janssen COVID-19 Vaccine EUA Letter of Authorization, Janssen will be required to report to VAERS:

- Serious adverse events (irrespective of attribution to vaccination);
- Cases of Multisystem Inflammatory Syndrome in adults; and
- Cases of COVID-19 that result in hospitalization or death that are reported to Janssen.[59]

Janssen must also submit to their IND periodic safety reports, at monthly intervals, that include a summary and analysis of adverse events submitted during the reporting interval, including by age groups, special populations (e.g., pregnant women), and adverse events of special interest; a summary and analysis of vaccine administration errors; newly identified safety concerns; and actions taken since the last report because of adverse experiences.[60] In addition, Janssen will conduct post-authorization observational studies to evaluate the association between Janssen COVID-19 Vaccine and a pre-specified list of adverse events of special interest, along with deaths and hospitalizations, and severe COVID-19.[61]

The Janssen COVID-19 Vaccine will also be subject to U.S. government monitoring systems, including VAERS, FDA's BEST System, and CDC's Vaccine Safety Datalink, as described in section II.B. of this response. For these reasons, FDA denies Petitioner's requests to require the Janssen clinical trial to document "any and all adverse events and reactions" for the specified periods of time prior to authorization.

2. Sample Size

Petitioner requests that the study design for the Ad26.COV2.S study be amended to provide that it "uses an adequate sample size, appropriately powered," to meet two goals: (1) "detect an increase in rare adverse events or any untoward medical occurrence, whether or not considered vaccine related," and (2) "determine that the rate of adverse events from the vaccine will not exceed the rate of adverse events known to occur from SARS-CoV-2 in the group under review." CP at 2.

[57] Id. at 12.
[58] Id. at 16-17.
[59] Janssen COVID-19 Vaccine EUA Letter of Authorization at 6.
[60] Id.
[61] Id. at 7.

Petitioner states that "[t]he study design for Ad26.COV2.S Vaccine provides for 30,000 individuals in the study group that will receive the Ad26.COV2.S Vaccine and 30,000 individuals will be in the control group that will receive the placebo," and asserts that "[a] Phase III trial for Ad26.COV2.S Vaccine with 30,000 subjects may not produce an adequate safety profile" for the vaccine. CP at 7. Petitioner further asserts that, because the percentage of individuals suffering "serious health issues" from SARS-CoV-2 is "statistically small on a population level," a "well-powered trial" is needed to assess the safety profile of the Ad26.COV2.S vaccine. CP at 7.

As a general matter, FDA evaluates study design of Phase 3 trials during the normal course of review of an IND, an EUA request, or a BLA. This review includes an evaluation of study plans and protocols regarding documentation and evaluation of adverse events. FDA has evaluated study plans and protocols of the Phase 3 trial of Ad26.COV2.S to help ensure that they are appropriate and adequate to ensure that the risks to participants are minimized and that the study can support authorization or licensure.

With regard to Petitioner's request that the Ad26.COV2.S trial use "an adequate sample size, appropriately powered, in order to…detect an increase in rare adverse events or any untoward medical occurrence, whether or not considered vaccine related" (CP at 7), we note that Petitioner has not pointed to any statistical analyses or other scientific literature demonstrating the inadequacy of the study that Petitioner identifies. We refer Petitioner to the June 2020 Guidance, in which FDA stated that the size of the safety database to support licensure of a vaccine to prevent COVID-19 should be no different than that for other preventive vaccines for infectious diseases.[62] The 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.[63] Petitioner asserts that "30,000 individuals [will be] in the study group that will receive the Ad26.COV2.S Vaccine and 30,000 individuals will be in the control group that will receive the placebo." CP at 7. We note that Janssen has made publicly available an amendment to the study protocol, in which the sponsor revised the total sample size from 60,000 to approximately 40,000 participants.[64] We point out that the resultant sample sizes of 20,000 subjects in the active arm and 20,000 in the control arm provide considerably more sensitivity to detect imbalances in rare adverse events than would the recommended minimum safety database size of 3,000 vaccinated individuals. In general, statistical hypothesis tests are not used to differentiate between true and spurious imbalances in unexpected adverse events in clinical trials. Instead, FDA reviewers investigate each adverse event imbalance, with statistical significance tests and confidence intervals sometimes used to flag imbalances of most concern. An event that occurs at a true rate of 1 per 1,000 unvaccinated individuals and 2.5 per 1,000 vaccinated individuals would be very likely to lead to a flagged imbalance in a clinical trial with 20,000 subjects per group (95% power). Because a trial of the size identified by Petitioner would be very likely to detect an imbalance in the occurrence of such an adverse event, we conclude that the size of the trial identified by Petitioner is adequate to support authorization of the vaccine at this time. Additional discussion of the statistical analysis of clinical trial safety data is provided in Section 6.4 of FDA's guidance document E9 Statistical Principles for Clinical

[62] June 2020 Guidance at 15.
[63] Id.
[64] Janssen Ad26.COV2.S Protocol, at 3.

Trials.[65] We conclude that Petitioner has not provided a basis for FDA to take any action with respect to the size of the study identified by Petitioner.

Petitioner further asserts that

> [e]ven 30,000 subjects in the group receiving the experimental vaccine may not be sufficient, according to a report from the Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research at the FDA, with regard to assessing safety of the Ad26.COV2.S Vaccine for anything other than the groups with the highest risk of complications from SARS-CoV-2.

CP at 7. Petitioner cites to the publication Safety Considerations for New Vaccine Development by Susan S. Ellenberg.[66]

Contrary to Petitioner's suggestion, the 2001 Ellenberg publication predates COVID-19 and addresses neither the Ad26.COV2.S clinical trial nor any other COVID-19 vaccine clinical trial. That publication, which states that vaccines are highly effective and extremely safe, advocates for large trials to detect rare adverse events and determine whether the rare adverse events are attributable to the vaccine or coincidental. Unlike Petitioner, Ellenberg does not advocate comparing rates of all adverse events and does not recommend different clinical trial designs for populations that may be affected by mild or severe disease. We agree with Ellenberg and Petitioner that larger clinical trials are generally more effective for identifying rare adverse reactions to vaccines. However, for the reasons given in this response, we disagree that the Ad26.COV2.S study is inadequate to demonstrate a safety profile that would support authorization.

With regard to Petitioner's request that the trial use "an adequate sample size, appropriately powered, in order to…determine that the rate of adverse events from the vaccine will not exceed the rate of adverse events known to occur from SARS-CoV-2 in the group under review" (CP at 7), we disagree that any such comparison of "rates" of adverse events is necessary or appropriate.

Petitioner's request relates to the manner in which FDA assesses risks and benefits of a vaccine based on clinical trial results. All vaccines are associated with some risk. FDA licenses or authorizes a vaccine after a careful assessment of its safety profile and a determination that the vaccine's benefits outweigh its potential risks for the indicated use in the indicated population. An assessment of risk is not as simple as merely tabulating the rate of any adverse events from a vaccine and the rate of adverse events for SARS-CoV-2. Among other things, FDA takes into account the *severity* of adverse events. For example, one expected adverse event from a vaccine might be soreness at the site of injection. Individuals who do not receive a vaccine would not, of course, experience such soreness. However, FDA does not consider soreness to be a *significant* adverse event that would justify withholding licensure or authorization of a vaccine to prevent disease. Petitioner does not offer any scientific justification for why a mere tabulation comparing the rate of any and all adverse events would be appropriate.

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[65] E9 Statistical Principles for Clinical Trials; Guidance for Industry, September 1998, https://www.fda.gov/media/71336/download

[66] Ellenberg, S., Safety considerations for new vaccine development, Pharmacoepidemiology and Drug Safety, 10: 411-415, 2001, https://pubmed.ncbi.nlm.nih.gov/11802587/.

Petitioner specifies that, "[f]or example, for children, the clinical trial should be properly sized and powered to determine that the vaccine is safer than a SARS-CoV-2 infection." CP at 2, footnote 4. In considering the risks and benefits of a vaccine, FDA considers the nature of the infection or disease that the product targets. But we do not agree that the comparison Petitioner describes is a necessary focus of study design for this or any other population.[67] In the June 2020 Guidance, FDA stated that the goal of development programs for vaccines to prevent COVID-19 should be to seek direct evidence of vaccine safety and efficacy in protecting humans from SARS-CoV-2 infection and/or clinical disease.[68] In other words, a vaccine would be licensed based on a demonstration of safety and effectiveness to prevent infection and/or COVID-19. Adequate data would be needed to support approval for a vaccine's use in children. Petitioner has not offered a scientific justification for the proposed approach for study design.

FDA's licensure or authorization of a vaccine is dependent upon a demonstration that the relevant statutory requirements have been met for the population indicated in the labeling.[69] The safety of vaccines such as Ad26.COV2.S is assessed by comparing the occurrence and frequency of local and systemic adverse events, including any that are serious, in the clinical trial participants who received the vaccine to the occurrence and frequency of these adverse events in the participants who received the control. Subjects in the vaccinated and control groups are monitored for safety, including for the occurrence of serious adverse events.[70] As noted above, a protocol with sample sizes of approximately 20,000 subjects in the active arm and 20,000 subjects in the control arm would provide for the study to be adequately powered to detect a statistically significant imbalance in the occurrence of an adverse event that occurs at a true rate of 1 per 1,000 unvaccinated individuals and 2.5 per 1,000 vaccinated individuals. In reviewing the EUA request, FDA found that the Ad26.COV2.S clinical study was of sufficient size and adequately powered to support an EUA for the populations specified in the Janssen COVID-19 Vaccine EUA Letter of Authorization.

Because Petitioner has not supported the requests related to the size of the Ad26.COV2.S clinical study, FDA denies the requests.

3. T-Cell Reactivity

Petitioner requests that "the study design for the Phase III trial of Ad26.COV2.S…be amended to provide that…participants are tested for T-cell reactivity to SARS-CoV-2 pre-vaccination and

[67] Petitioner appears to believe that COVID-19 does not pose serious health concerns for young people, asserting that "SARS-CoV-2 poses a statistically insignificant risk of harm to children and young healthy adults." CP at 7. FDA points out that COVID-19 can be a severe disease in any age group. Although fewer children have been sick with COVID-19 compared to adults, and most children with COVID-19 have mild symptoms or have no symptoms, some children can become severely ill. Such children may require hospitalization, intensive care, or a ventilator; in rare cases, they might die. In addition, children under one year old and children with certain underlying conditions may be more likely to have severe illness from COVID-19. CDC, COVID-19 in Children and Teens, updated December 2020, https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/symptoms.html.

[68] June 2020 Guidance at 2.

[69] It is important to note that, when evaluating the safety and effectiveness of a vaccine, FDA considers characteristics of both the population to receive the vaccine and the disease(s) to be prevented. With regard to COVID-19 vaccines and pediatric populations, FDA has advised that developers of COVID-19 vaccines should plan for pediatric assessments of safety and effectiveness. June 2020 Guidance at 11. In authorizing or licensing a vaccine to prevent COVID-19 for use in any population, FDA will determine the safety and effectiveness of that vaccine in that population.

[70] FDA Janssen COVID-19 Vaccine Briefing Document at 17.

post-vaccination." CP at 2. In support of this request, Petitioner quotes an article in which the authors state that "if subjects with pre-existing reactivity were sorted unevenly in different vaccine dose groups, this might lead to erroneous conclusions. Obviously, this could be avoided by considering pre-existing immunity as a variable to be considered in trial design."[71,72] CP at 8.

The authors of the article cited by Petitioner state that "[i]t is frequently assumed that pre-existing T cell memory against SARS-CoV-2 might be either beneficial or irrelevant. However, there is also the possibility that pre-existing immunity might actually be detrimental."[73] FDA agrees that the implications of T-cell reactivity are not yet well-understood, and it is unclear at this time whether or how T-cell reactivity would impact the results of the clinical trial. Insofar as T-cell reactivity could be a confounding variable that could bias the comparison between the placebo and active vaccine groups, randomization would be an appropriate strategy to minimize any variability. Participants in this study are randomized to the active vaccine and the placebo control groups, ensuring that the groups are balanced with regard to identified and unidentified confounders.[74] We are not aware of any basis to conclude that any preexisting T-cell reactivity among study participants undercuts the comparability between the placebo and active vaccine groups. Therefore, requiring testing for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination would not provide meaningful information for purposes of FDA's authorization or licensure of a vaccine to prevent COVID-19.[75]

For the foregoing reasons, FDA denies Petitioner's request to require Janssen to conduct such testing in the Ad26.COV2.S clinical study.

4. Germline Transmission Tests

Petitioner requests that "the study design for the Phase III trial of Ad26.COV2.S…be amended to provide that…germline transmission tests are conducted for male participants." CP at 2.

To support this request, Petitioner relies upon a 2006 guideline published by the European Medicines Agency's Committee for Medicinal Products for Human Use, Guideline on Non-Clinical Testing for Inadvertent Germline Transmission of Gene Transfer Vectors (2006 EMA

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[71] Sette, A. and Crotty, S. Pre-existing immunity to SARS-CoV-2: the knowns and unknowns, Nat Rev Immunol 20, 457–458 (2020), https://www.nature.com/articles/s41577-020-0389-z.

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

> Pre-existing $CD4^+$ T cell memory could also influence vaccination outcomes, leading to a faster or better immune response, particularly the development of neutralizing antibodies, which generally depend on T cell help. At the same time, pre-existing T cell memory could also act as a confounding factor, especially in relatively small phase I vaccine trials. For example, if subjects with pre-existing reactivity were assorted unevenly in different vaccine dose groups, this might lead to erroneous conclusions. Obviously, this could be avoided by considering pre-existing immunity as a variable to be considered in trial design. Thus, we recommend measuring pre-existing immunity in all COVID-19 vaccine phase I clinical trials.

Id. at 458.

[73] Id. at 457–458.

[74] FDA Janssen COVID-19 Vaccine Briefing Document at 6.

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

Guideline).[76] Petitioner states that "viral or non-viral vectors may be associated with a risk of vertical germline transmission of vector DNA" and quotes the 2006 EMA Guideline to state that "[w]hile 'currently there are no non-invasive means to monitor women for germline transmission,' male participants in the clinical trials can and should be monitored." CP at 8. Petitioner further quotes the 2006 EMA Guideline to state that

> "[s]ince one cycle of spermatogenesis takes approximately 64-74 days in man, the timing of the appearance of transduced progenitor daughter cells in the semen is predictable. This can be taken into account in the planning of germline transmission tests as part of clinical trial protocols."[] Further, "this can be accomplished by investigating sperm at different time points taking into account the duration of spermatogenesis.

CP at 8.

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, testing 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.[77] With respect to the vector, the 2006 EMA Guideline states that assessment of risk should be based on the vector's biodistribution profile, vector replication, and integration ability.[78] In addition, a Considerations document issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use[79] (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.[80]

[76] 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.
[77] Id. at 5.
[78] Id.
[79] Now the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
[80] ICH Considerations, 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.

This ICH Considerations document further states: "[i]f, 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."[81]

Petitioner's request applies, specifically, to the Phase 3 trial of Ad26.COV2.S. The Janssen COVID-19 Vaccine is a monovalent vaccine composed of a recombinant adenovirus serotype 26 (Ad26) vector, constructed to contain genetic information encoding the spike (S) protein of SARS-CoV-2.[82] For this vector, the E1 region of the adenoviral genome, which encodes proteins required for virus replication, is deleted, rendering the vector replication-incompetent.[83] 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.[84] 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. For these reasons, FDA does not consider that this vaccine poses a risk of vertical germline transmission of vector DNA. Therefore, FDA denies Petitioner's request to require Janssen to modify the Phase 3 protocol to include germline transmission studies for male participants in the Ad26.COV2.S clinical trial, and we do not believe that there is a scientific need for such testing to be a condition of the EUA for the Janssen COVID-19 Vaccine.

5. HIV Incidence Monitoring

Petitioner requests that

> the study design for the Phase III trial of Ad26.COV2.S…be amended to provide that…HIV incidence will be "monitored at the end of the study and for an appropriate follow-up period"[] and the trial will "evaluate the levels and distribution of both vector and insert responses in target tissues where HIV acquisition is known to occur."

CP at 2.

Petitioner states that "[t]he Ad26.COV2.S is a recombinant viral vector vaccine. In past viral vector vaccine clinical trials, HIV incidence was higher in vacinees [sic] than in placebo recipients." CP at 9. Petitioner references the 2008 publication by Buchbinder et al. (the Step Study),[85] describing it as follows:

> a multicenter, double-blind, randomized, placebo-controlled phase II test of concept study of a trial HIV vaccine. The vaccine consisted of a 1:1:1 mixture of 3 separate replication-defective Ad5 vectors…As pre-specified in the protocol, an interim analysis of HIV incidence and early HIV-1 viral load was conducted. This analysis showed that HIV incidence was higher in the vaccine group than in the placebo group…HIV rates

[81] Id. at 3.
[82] Janssen Ad26.COV2.S Protocol at 10.
[83] Id. at 38.
[84] 2006 EMA Guideline at 4.
[85] Buchbinder, S., Mehrotra, D., Duerr, A., et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): A double-blind, randomised, placebo-controlled, test-of-concept trial, Lancet 372(9653), 1881-1893 (2008) (the Step Study), https://pubmed.ncbi.nlm.nih.gov/19012954/.

> appeared to be more than twice as high in vaccinees compared with placebo recipients in Ad5 seropositive men.

CP at 9.

Petitioner also references a 2014 publication by Fauci et al. that summarizes the experience with recombinant Ad5-vectored HIV vaccines, including the Step Study.[86] Quoting from that publication, Petitioner states:

> For non-HIV vaccine trials using vectors that induce strong T-cell immunity… it may be important to monitor for HIV acquisition, depending on the target population. In such studies where the population may be at risk of HIV exposure, HIV incidence should be monitored at the end of the study and for an appropriate follow-up period.

CP at 9; emphasis omitted.[87] Petitioner concludes that, "[a]lthough the Ad26.COV2.S Vaccine is not specifically an Ad-5 vector vaccine, the principle still stands: an adenovirus-based vaccine that may potentially 'induce strong T-cell immunity' must be evaluated in order to determine whether or not it makes vacinees [sic] more susceptible to contracting HIV." CP at 9.

Quoting from the 2014 publication by Fauci et al., Petitioner states that "[f]uture clinical testing of Ad-based vaccines should evaluate the levels and distribution of both vector and insert responses in target tissues where HIV acquisition is known to occur" (emphasis omitted). CP at 9. Petitioner asserts that "[o]ther studies evidence that the appropriate target tissues to be evaluated are mucosal tissues." CP at 9. To support this statement, Petitioner quotes from a 2010 publication by Liu[88] in which the author addresses the Step Study:

> One possible explanation for these [Step Study] results [higher incidence of HIV in vaccines than placebo group], aside from it being stochastic, is that in patients with high anti-Ad5 titers, (i.e., presumably indicative of prior infection with adenovirus 5, and hence also with pre-existing Ad5 T helper cell responses) activated Ad5-specific T cells were more susceptible to infection by HIV… a further study showed that when T cells from individuals who had pre-existing antibodies against adenovirus were stimulated with adenovirus, an increase in memory CD4+T cells occurred, and these T cells were more easily infected with HIV. In addition, these T cells homed to mucosa, which could provide an explanation for the results of the two prior studies that had sampled peripheral blood lymphocytes rather than mucosal lymphocytes. These studies highlighted, among other issues, that many of the read-outs of immunologic parameters have utilized peripheral blood lymphocytes, which may not reflect cells or immune conditions in organs or at the sites of infection

(emphasis omitted; internal references omitted by Petitioner). CP at 10. Petitioner asserts that "in evaluating the HIV incidence in trial participants, mucosal lymphocytes are the appropriate target tissues to test." CP at 10.

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[86] Fauci, A., Marovich, M., Dieffenbach, C., et al. Immune activation with HIV vaccines, Science 344(6179), 49-51 (2014), https://pubmed.ncbi.nlm.nih.gov/24700849/.

[87] We note that the full quote by Fauci et al. in the 2014 publication specifies "[f]or non-HIV vaccine trials using vectors that induce strong T cell immunity that are conducted in regions with high HIV incidence, it may be important to monitor for HIV acquisition, depending on the target population" (emphasis added). Id. at 51.

[88] Liu, M. Immunologic basis of vaccine vectors, Immunity 33(4), 504-515 (2010), https://pubmed.ncbi.nlm.nih.gov/21029961/.

Finally, Petitioner quotes a 2015 publication by Fauci and Marston[89]:

> Unfortunately, two phase IIb trials (STEP and Phambili) testing a candidate that expressed HIV *gag*, *pol*, and *nef* were halted after interim Data and Safety Monitoring Board reviews revealed poor efficacy. In fact, the trials demonstrated evidence of increased risk of viral acquisition among vaccine recipients as compared with placebo. A scientific symposium reviewing those data concluded that vaccine-related immune activation might have led to increased susceptibility to infection.

(emphasis omitted; internal reference omitted by Petitioner). CP at 10.

Petitioner concludes, "Petitioner therefore requests that the incidence of HIV be assessed in trial participants at the end of the trial, and for an appropriate follow-up period after the trial, and also that the evaluations are completed in appropriate mucosal target tissues." CP at 10.

As stated above, the Janssen COVID-19 Vaccine is based on an Ad26 vector that expresses the SARS-CoV-2 spike protein.

Petitioner's support for the request that the study design for the Phase III trial of Ad26.COV2.S be amended to provide for monitoring of HIV incidence centers on the Step Study, a clinical trial designed to evaluate an investigational HIV vaccine administered to individuals at high risk of HIV-1 acquisition.[90] CP at 9. In that trial, the investigational HIV vaccine consisted of a mixture of three separate replication-defective adenovirus serotype 5 (Ad5) vectors, each expressing a different HIV-1 gene.[91] Exploratory analyses of data from the Step Study found that acquisition of HIV was higher in participants receiving the vaccine than in participants receiving placebo among men with prior evidence of Ad5 infection and among uncircumcised men.[92] The reason for the observed increase in HIV in these populations remains uncertain.

It is not evident that the increase in HIV acquisition observed in these populations in the Step Study would implicate all adenoviral vector vaccines. As Fauci et al. point out in the 2014 publication cited by Petitioner, their analysis addresses Ad5-based HIV vaccines specifically:

> The experience with rAd5-based HIV vaccines has shown that vaccine-induced protection likely reflects the balance between beneficial anti-HIV responses and deleterious effects of immune activation that increases the susceptibility of $CD4^+$ T cells to infection…Among the spectrum of existing or planned vaccines, this phenomenon is likely unique for an HIV vaccine because the activated $CD4^+$ T cell is the very target for the virus. These observations should be taken into consideration in future HIV vaccine research endeavors and underscores the importance of maximizing the specific anti-HIV responses of such candidates

[89] Fauci, A. and Marston, H. Toward an HIV vaccine: A scientific journey, Science 349(6246), 386-387 (2015), https://science.sciencemag.org/content/349/6246/386.summary.
[90] Buchbinder, S., Mehrotra, D., Duerr, A., et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): A double-blind, randomised, placebo-controlled, test-of-concept trial, Lancet 372(9653), 1881-1893 (2008), https://pubmed.ncbi.nlm.nih.gov/19012954/.
[91] Id. at 1882.
[92] Id. at 1891.

(emphasis added).[93] Their analysis does not extend to other adenoviral vaccines that express other proteins, such as the Janssen COVID-19 Vaccine, which is based on an Ad26 vector that expresses the SARS-CoV-2 spike protein.

FDA disagrees with Petitioner's assertion, apparently based on the 2014 publication by Fauci et al., that "an adenovirus-based vaccine that may potentially 'induce strong T-cell immunity' must be evaluated in order to determine whether or not it makes vacinees [sic] more susceptible to contracting HIV." CP at 9. We are not aware of data suggesting that the increased HIV-1 infection rate observed in the Step Study would be expected with vaccines that do not contain Ad5 vectors expressing HIV proteins.

Petitioner's request that the study design for the Phase III trial of Ad26.COV2.S be amended to provide for monitoring of HIV incidence seems to be based on the idea that any immune response induced by a viral vector vaccine is necessarily a cause for concern with respect to HIV acquisition. However, we note that Correspondence published in The Lancet in October 2020, written by several of the co-authors of studies cited by Petitioner, suggests that, although the adenovirus serotype 5-vectored HIV vaccine induced HIV-specific CD4 and CD8 T-cells, differences in the immune response was not the mechanism of increased HIV acquisition:

> The vaccine was highly immunogenic in the induction of HIV-specific CD4 and CD8 T cells; however, there was no difference in the frequency of T-cell responses after vaccination in men who did and did not later become infected with HIV in the Step Study.[][94]

The finding that there were no differences in the magnitude of HIV-specific T-cell responses among those who later became infected with HIV in the Step Study indicates that these HIV-specific T-cell responses alone were not responsible for increases in HIV acquisition. It appears that baseline characteristics of the population are also relevant, specifically whether participants had preexisting antibodies to the Ad5 viral vector. The 2010 publication by Liu referenced by Petitioner states:

> However, one result that came out of the [Step Study] was that more individuals who had high titers of adenovirus antibodies before being immunized became HIV infected than did similar patients who received the placebo. No differences in rates of HIV infection were seen in patients receiving vaccine or placebo in individuals who had low pre-existing adenovirus antibody titers.[95]

This indicates that, in the context of HIV antigen presentation, the use of an Ad5 vector in the context of high prior titers of Ad5 antibodies was associated with increased risk of HIV acquisition. Thus, the mechanism of increased risk in the Step Study appeared to require both the presence of HIV antigen and the use of an Ad5 vector. Of note, the results of the Step Study

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[93] Fauci, A., Marovich, M., Dieffenbach, C., et al. Immune activation with HIV vaccines, Science 344(6179), 49-51 (2014), at 51, https://science.sciencemag.org/content/344/6179/49.long.

[94] Buchbinder, S., McElrath, M., Dieffenbach, C, et al. Use of adenovirus type-5 vectored vaccines: A cautionary tale. Correspondence, Lancet 396(10260), e68-e69 (2020), at e68, https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2932156-5.

[95] Liu, M. Immunologic basis of vaccine vectors, Immunity, 33(4), 504-15 (2010), at 507, https://pubmed.ncbi.nlm.nih.gov/21029961/.

were replicated in a 2012 study using simian immunodeficiency virus (SIV) in macaques.[96] SIV is similar to HIV, and SIV infection of macaques serves as an animal model of HIV infection and disease. In this animal study, there was evidence of a greater risk of infection only in Ad5-seropositive animals (that is, animals that were seropositive prior to vaccination) immunized with an Ad5 vaccine similar to that used in the Step Study.[97] The study showed no evidence of enhanced susceptibility to SIV following penile exposure in the Ad5-seropositive non-human primates (NHPs) immunized with the Ad5 vector alone. The authors hypothesize that

> vaccine-induced vector-specific immune responses did not contribute to altered susceptibility to SIV in the immunized NHP. Rather, it seems that vaccine-induced SIV-specific immune responses are responsible for the enhanced susceptibility in Ad5-seropositive, immunized NHP. Further, as with the Step Trial, this effect was not seen in the immunized animals that were Ad5 seronegative at immunization

(emphasis added).[98]

The authors also point out that "[t]he hypothesis that Ad5-specific immunity does not explain the results of the Step Trial is supported by the results of a recent case-control study that found no evidence that Ad5 seropositivity increases susceptibility to HIV infection[99]" (footnote renumbered).[100]

Therefore, while explanations for the apparent enhanced risk of HIV acquisition among Ad5-seropositive vaccine recipients in the Step Study remain uncertain, available evidence suggests that the enhanced risk observed in that study required both an HIV antigen to be expressed and the use of an Ad5 vector. Therefore, FDA would not consider the use of an adenovirus vector in a vaccine, in and of itself, to necessitate monitoring for effects of a non-HIV vaccine on HIV acquisition. Furthermore, Petitioner has not provided evidence that the Ad26 vector used in the Janssen COVID-19 Vaccine is linked to enhanced susceptibility to HIV infection for the population indicated in the labeling. Therefore, FDA denies Petitioner's request to require Janssen to modify the protocol for the Phase 3 trial of Ad26.COV2.S to include monitoring of participants for HIV acquisition and evaluation of levels and distribution of vector and insert responses in mucosal lymphocytes or other target tissues. In addition, FDA does not believe that such changes to the study protocol should be a condition of the issuance of an EUA for the Janssen COVID-19 Vaccine.

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[96] Qureshi, et al. Low-dose penile SIVmac251 exposure of rhesus macaques infected with adenovirus type 5 (Ad5) and then immunized with a replication-defective Ad5-based SIV *gag/pol/nef* vaccine recapitulates the results of the Phase IIb Step Trial of a similar HIV-1 vaccine, Journal of Virology, 86(4), 2239-2250 (2012), https://pubmed.ncbi.nlm.nih.gov/22156519/.

[97] Id.

[98] Id. at 2247.

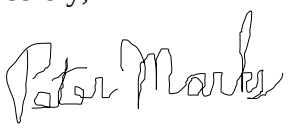
[99] Curlin, M., Cassis-Ghavami, F., Magaret, A., et al. Serological immunity to adenovirus serotype 5 is not associated with risk of HIV infection: A case-control study, AIDS 25(2), 153-158 (2011), https://pubmed.ncbi.nlm.nih.gov/21150554/.

[100] Qureshi, H., Ma, Z-M., Huang, Y., et al. Low-dose penile SIVmac251 exposure of rhesus macaques infected with adenovirus type 5 (Ad5) and then immunized with a replication-defective Ad5-based SIV *gag/pol/nef* vaccine recapitulates the results of the Phase IIb Step Trial of a similar HIV-1 vaccine. J Virol 86(4), 2239-2250 (2012), at 2247, https://pubmed.ncbi.nlm.nih.gov/22156519/.

IV. Conclusion

FDA has considered Petitioner's requests relating to the clinical trial of the Ad26.COV2.S vaccine to prevent COVID-19. For the reasons given in this letter, FDA denies the requests and therefore denies the CP in its entirety.

Sincerely,



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

cc: Dockets Management Staff

Appendix I: Aspects of Vaccine Development and Process for Licensure

A. Vaccines are Biologics and Drugs

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

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

B. Clinical Investigations of Vaccines

Before a vaccine is licensed (approved) by FDA and can be used by the public, FDA requires that it undergo a rigorous and extensive development program that includes laboratory research, animal studies, and human clinical studies to determine the vaccine's safety and effectiveness.

The PHS Act and the FD&C Act provide FDA with the authority to promulgate regulations that provide a pathway for the study of unapproved new drugs and biologics. 42 U.S.C. § 262(a)(2)(A) and 21 U.S.C. § 355(i). The regulations on clinical investigations require the submission of an Investigational New Drug application (IND), which describes the protocol, and, among other things, assures the safety and rights of human subjects. These regulations are set out at 21 CFR Part 312. See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).

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

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

C. Biologics License Applications

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

Under § 601.2(a), FDA may approve a manufacturer's application for a biologics license only after the manufacturer submits an application accompanied by, among other things, "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency." The BLA must provide the multidisciplinary FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc.) with the Chemistry, Manufacturing, and Controls (CMC)[101] and clinical information necessary to make a benefit-risk assessment, and to determine whether "the establishment(s) and the product meet the applicable requirements established in [FDA's regulations]." 21 CFR § 601.4(a).

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

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

As part of FDA's evaluation of a vaccine as a whole, FDA takes all 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.

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

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. 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.