December 18, 2020

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

Re: Citizen Petitions and Petition for Administrative Stay of Action (Docket Number FDA-2020-P-1769)

Dear Mr. Siri,

This letter responds to the following citizen petitions and petition for administrative stay of action that you submitted to the Food and Drug Administration (FDA, the Agency, we) on behalf of Del Bigtree and the Informed Consent Action Network (ICAN) (Petitioner) relating to the clinical trial of mRNA-1273, a vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2):

- The citizen petition dated August 17, 2020 (the CP);[1]
- The petition for administrative stay of action dated August 19, 2020 (the PSA); and
- The amended citizen petition dated October 16, 2020 (the Amended CP) [2]

(collectively, the Petitions).[3]

In the CP, Petitioner requests FDA to cause "the study design for the Phase III trial of mRNA-1273 (NCT04470427)" to be amended to provide that:

a. any and all adverse events and reactions[] will be documented for the entire duration of the trial;

[1] This submission is entitled "Citizen Petition"; however, it also states that "[t]his petition for administrative action is submitted…pursuant to 21 CFR § 10.35" (Petitions for administrative stay of action). CP at 1. For purposes of this response, we are treating this as a citizen petition submitted under 21 CFR § 10.30. The requested actions and formatting of the submission are consistent with citizen petitions submitted under 21 CFR § 10.30.
[2] This submission is entitled "Amended Citizen Petition" and references the CP. Amended CP at 1. However, it also states that "[t]his amended petition for administrative action is submitted…pursuant to 21 CFR § 10.35" (Petitions for administrative stay of action). Id. at 2. For purposes of this response, we are treating this as a citizen petition submitted under 21 CFR § 10.30. The requested actions and formatting of the submission are consistent with citizen petitions submitted under 21 CFR § 10.30.
[3] 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-1770, FDA-2020-P-2096, and FDA-2020-P-2180. FDA either has responded or is responding separately to those petitions.

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b. such documenting of adverse events and reactions shall last at least twelve months for adults, thirty-six months for children, and sixty months for infants and toddlers;
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;[] and
d. participants are tested for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination.

CP at 2.

In the PSA, Petitioner requests FDA to:

> [s]tay the Phase III trial of mRNA-1273 (NCT04470427) until its study design is amended to provide that:
>
> a. any and all adverse events and reactions[] will be documented for the entire duration of the trial;
>
> b. such documenting of adverse events and reactions shall last at least twelve months for adults, thirty-six months for children, and sixty months for infants and toddlers;
>
> 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;[] and
>
> d. participants are tested for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination.

PSA at 2.

In the Amended CP, Petitioner reiterates the requests in the CP with a revision regarding the documentation of adverse events (request "b") to request 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." Amended CP at 2 (emphasis added).

This letter responds to the Amended CP and the PSA in full.[4] We have carefully reviewed the Petitions, comments submitted to the docket, and other information available to the Agency. Based on our review of these materials and for the reasons described below, we conclude that the

[4] The Agency interprets the Amended CP to supersede the CP in light of Petitioner's statements that "[t]he original petition in this matter was submitted on August 17, 2020" and "it appears that some of Petitioner's conditions have been met and Petitioner therefore submits this amended petition to address the outstanding conditions." Amended CP at 1. To the extent that Petitioner did not intend for the Amended CP to supersede the CP, the responses in this letter also pertain to the actions requested in the CP.

Petitions do not contain facts demonstrating any reasonable grounds for the requested action. In accordance with 21 CFR §§ 10.30(e)(3) and 10.35(e), and for the reasons stated below, FDA is denying the Petitions.

Here is an outline of our response:

I. Background

There is currently a pandemic of respiratory disease, 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.[5] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[6] 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

[5] 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.
[6] 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/.

underway. On November 30, 2020, ModernaTX, Inc. (Moderna) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine, mRNA-1273, intended to prevent COVID-19.[7] As announced by FDA on December 18, 2020, the Agency is granting EUA for the Moderna COVID-19 Vaccine.[8]

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.[9,10] 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."[11] 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.[12]

As is evident from the language of the PHS Act and FDA's regulations, the licensure process for a vaccine requires the sponsor to establish, through carefully controlled laboratory and clinical studies, as well as through other data, that the product is safe and effective for its approved indication(s) and use. FDA's multidisciplinary review teams then rigorously evaluate the sponsor's laboratory and clinical data, as well as other information, to help assess whether the safety, purity, and potency of a vaccine has been demonstrated.[13] 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."[14] 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

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[7] FDA Briefing Document, Moderna COVID-19 Vaccine, Vaccines and Related Biological Products Advisory Committee Meeting, December 17, 2020, at 5 (FDA Moderna COVID-19 Vaccine Briefing Document), https://www.fda.gov/media/144434/download.
[8] FDA EUA Letter of Authorization for the Moderna COVID-19 Vaccine dated December 18, 2020 (Moderna COVID-19 Vaccine EUA Letter of Authorization), https://www.fda.gov/media/144636/download.
[9] 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.
[10] Vaccine Safety Questions and Answers, last updated March 2018, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers.
[11] 42 U.S.C. § 262(a)(2)(C)(i)(I).
[12] 21 CFR § 601.2(a).
[13] Vaccines, last updated June 2020, https://www.fda.gov/vaccines-blood-biologics/vaccines.
[14] 21 CFR § 601.2(d) (emphasis added).

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.[15] On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564(b)(1) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)).[16]

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

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[15] 85 FR 7316, February 7, 2020, https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency.

[16] 85 FR 18250, April 1, 2020, https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration.

- The agent referred to in the March 27, 2020 EUA declaration by the Secretary (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.[17] 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.[18] 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.[19]

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

In a Phase 3 study of a COVID-19 vaccine, the efficacy of the investigational vaccine to prevent disease will be assessed by comparing the number of cases of disease in each study group. For Phase 3 trials, FDA has recommended to manufacturers in guidance that the vaccine should be at least 50% more effective than the comparator, and that the outcome be reliable enough so that it is not likely to have happened by chance.[20] During the entire study, subjects will be monitored

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

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.[21] 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.[22] 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.

III. Discussion

The Petitions pertain to the study design for "the Phase III trial of mRNA-1273" (Amended CP at 2; PSA 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.[23]

[21] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022; https://www.fda.gov/media/99140/download.
[22] October 2020 Guidance at 10.
[23] See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).

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[24]) 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.[25] The IND describes the proposed clinical study in detail and, among other things, helps protect the safety and rights of human subjects.[26] 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),[27] and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials, unless FDA informs the sponsor that the trial may begin earlier. During this time, FDA reviews the IND. FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and Phase 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.[28]

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.

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[24] 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.

[25] See 21 CFR § 312.20(a).

[26] 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.

[27] 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.

[28] 21 CFR § 312.22(a).

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.[29]

B. The Citizen Petition

In the Amended CP, Petitioner requests that FDA amend "the Phase III trial of mRNA-1273 SARS-CoV-2 (NCT04470427)" to have certain design characteristics relating to the documentation of adverse events, sample size, and testing for T-cell reactivity to SARS-CoV-2.[30] Amended CP at 2. Because FDA does not itself create or amend drug investigations,[31] we interpret the Amended CP as asking that FDA require the sponsors to make the requested changes.[32] 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.[33]

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[29] 21 CFR § 312.42(a).

[30] The Agency notes that Petitioner "incorporates by reference…the Statement of Grounds from its Amended Citizen's Petition, dated July 20, 2020." Amended CP at 3, fn. 6. The July 20, 2020 Amended Citizen Petition (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 mRNA-1273 clinical trial (the subject of the Amended CP) specifically, we have considered the Statement of Grounds from the July 20, 2020 Amended Citizen Petition in responding to these petitions.

[31] 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.

[32] 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.

[33] 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-

1. Adverse Event Documentation

Petitioner asks FDA to require that the study design for the Phase 3 trial of mRNA-1273 document "any and all adverse events and reactions…for the entire duration of the trial" (Amended CP at 2), specifying 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.

Amended CP at 2, fn. 4.

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." Amended CP at 2.

Because the Amended 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 mRNA-1273 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 different than for other preventive vaccines for infectious diseases."[34] 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

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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." Amended 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 mRNA-1273, that is authorized or approved meets all relevant statutory requirements.

[34] June 2020 Guidance at 15.

> monitoring may be warranted for certain vaccine platforms (e.g., those that include novel adjuvants).[35]

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).[36]

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" (Amended CP at 2), which Petitioner states:

> [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.

Amended CP at 2, fn. 4.

In support of this request, Petitioner identifies what he characterizes as deficiencies with the safety follow-up procedures in the publicly-available mRNA-1273 protocol. Petitioner asserts that:

[35] Id.
[36] October 2020 Guidance at 10.

> [t]he current study design for mNRA-1273 [sic] provides that 'adverse events'… should be captured for only 28 days post-vaccination while 'serious adverse events'… and 'medically attended adverse events' that lead to an unscheduled visit to a healthcare practitioner (but excluding adverse events that lead to a scheduled medical visit) … should continue to be captured throughout the study.

Amended CP at 4. Petitioner also states that:

> [d]espite reviewing efficacy for at least 2 years, the current trial design for this vaccine will only capture 'systemic adverse events' for 7 days after each dose and 'unsolicited adverse events' (and medical [sic] attended adverse events that are noted during or lead to a scheduled medical visit) for only 28 days after each dose.

Amended CP at 4. Petitioner continues that "[i]ncredibly, beyond these extremely short safety review periods, an [adverse event] will only be captured if it results in the study participant withdrawing from the study." Amended CP at 4-5. Elsewhere, however, Petitioner acknowledges that adverse events will be captured beyond 28 days after dosing "if the adverse event is deemed 'serious' or 'medically attended.'" Amended CP at 3. Petitioner also asserts that "[g]iven that [serious adverse events] and [medically attended adverse events] leading to unscheduled medical visits are already being captured throughout the trial, it appears foolhardy to not also capture *all* adverse events during this period." Amended CP at 5.

Because Petitioner takes issue with the safety follow-up procedures in the mRNA-1273 clinical trial, it is helpful to identify what those procedures in fact are. The safety follow-up for the clinical trial, as described in the publicly-available mRNA-1273 protocol, includes, for each participant, monitoring and recording of: solicited local and systemic adverse reactions that occur during the 7 days following each injection using eDiaries; unsolicited adverse events observed or reported during the 28 days following each injection; adverse events leading to discontinuation from Day 1 through Day 759 or withdrawal from the study; medically-attended adverse events from Day 1 through Day 759 or withdrawal from the study; and serious adverse events from Day 1 through Day 759 or withdrawal from the study.[37] Thus, the planned safety follow-up includes monitoring for certain adverse events for two years and is not limited to situations in which the study participant withdraws from the study.

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.[38] For these types of safety data, it is generally important to collect information on all occurrences to better understand causality, incidence, severity of adverse

[37] The safety follow-up procedures are described in the FDA Moderna COVID-19 Vaccine Briefing Document at 16. In addition, the procedures are described in the protocol, dated August 20, 2020, that Moderna made publicly available: A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 RNA Vaccine in Adults Aged 18 Years and Older, at 12, https://www.modernatx.com/sites/default/files/mRNA-1273-P301-Protocol.pdf.

[38] Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations; Guidance for Industry, February 2016, at 6, https://www.fda.gov/media/82664/download.

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

Comprehensive safety data, including essentially all adverse events, are collected in the early stages of drug development.[42] 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.[43]

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 mRNA-1273 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 uninterpretable reports ("noise") in the system. Selective safety data collection in late-stage premarket clinical investigations is consistent with FDA's overall approach to safety assessment, which focuses on information that is useful and adds to existing knowledge.[44]

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

[39] Id. at 7.
[40] See Establishment and Operation of Clinical Trial Data Monitoring Committees; Guidance for Clinical Trial Sponsors, March 2006, https://www.fda.gov/media/75398/download.
[41] June 2020 Guidance at 15.
[42] Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations; Guidance for Industry, February 2016, at 2, https://www.fda.gov/media/82664/download.
[43] Id.
[44] Id. at 3.

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 mRNA-1273 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.[45] 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 medically attended adverse events for at least 6 months after completion of all study vaccinations.[46]

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.[47] 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.[48] Adverse events considered plausibly linked to vaccination generally start within 6 weeks after vaccine receipt.[49] Two months of follow-up should, therefore, provide time for potential

[45] Premarketing Risk Assessment; Guidance for Industry, March 2005 at 9; https://www.fda.gov/media/71650/download.
[46] June 2020 Guidance at 15.
[47] October 2020 Guidance at 10.
[48] Id.
[49] Health Resources and Services Administration, Vaccine Injury Table, 2017, https://www.hrsa.gov/sites/default/files/vaccinecompensation/vaccineinjurytable.pdf.

immune-mediated adverse events that began within this 6-week period to be observed and evaluated.

For an EUA for a COVID-19 vaccine, FDA's recommendation for a median follow-up period of at least 2 months after the final vaccine dose is based on extensive historical experience with vaccines, the need for a vaccine to address the current pandemic, and the magnitude of vaccine effectiveness that will be required to support a favorable benefit-risk profile for use of a COVID-19 vaccine under an EUA. 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 Amended CP that the mRNA-1273 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 30,351 participants with a median of 7 weeks of follow-up following the second dose, as well as additional safety data from these participants after a median of 9 weeks of follow-up following the second dose.[50] This follow-up period is justified based on the need for a vaccine to address the current pandemic and the magnitude of vaccine effectiveness that was demonstrated to support the favorable benefit-risk profile for the use of the vaccine under an EUA. Therefore, we deny the request to require a 24-month follow-up period for adults, and we do not believe this must be a condition of authorization for the mRNA-1273 COVID-19 vaccine.

Regarding Petitioner's request that FDA require, at this time, that the mRNA-1273 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.[51] 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. Amended CP at 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 mRNA-1273 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

[50] FDA has reviewed the safety data from the interim analysis with a median 7-week follow-up and the later submission covering a median 9-week follow up and has found the safety conclusions to be consistent. For a more complete description of FDA's safety evaluation, see the Moderna COVID-19 Vaccine Emergency Use Authorization Review Memorandum.

[51] We also note that, for mRNA-1273, Moderna'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 Moderna COVID-19 Vaccine EUA Letter of Authorization.

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.[52]

FDA has considered the periods of time over which the mRNA-1273 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 mRNA-1273 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.[53] FDA's June 2020 Guidance advises that follow-up of study participants for COVID-19 outcomes should continue as long as feasible, ideally at least one to two years.[54] 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.[55]

As will be the case for any COVID-19 vaccine, the mRNA-1273 vaccine will be subject to robust safety monitoring after authorization. The mRNA-1273 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 publicly-available Moderna COVID-19 Vaccine EUA Letter of Authorization, Moderna will be required to report to VAERS:

- Vaccine administration errors whether or not associated with an adverse event;
- Serious adverse events (irrespective of attribution to vaccination);
- Cases of Multisystem Inflammatory Syndrome in adults; and

[52] Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations; Guidance for Industry, February 2016, at 3, https://www.fda.gov/media/82664/download.
[53] June 2020 Guidance at 16.
[54] Id. at 12.
[55] Id. at 16-17.

- Cases of COVID-19 that result in hospitalization or death that are reported to Moderna.[56]

Moderna 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; newly identified safety concerns; and actions taken since the last report because of adverse experiences.[57] In addition, Moderna will conduct post-authorization observational studies to evaluate the association between Moderna COVID-19 Vaccine and a pre-specified list of adverse events of special interest, along with deaths and hospitalizations, and severe COVID-19.[58]

The Moderna 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 mRNA-1273 clinical trial of the 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 mRNA-1273 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." Amended CP at 2.

Petitioner states that "[t]he study design for mRNA-1273 provides for only 30,000 individual study subjects, which presumably means only 15,000 individuals will be in the study group that will receive mRNA-1273 and 15,000 individuals will be in the control group that will receive a placebo," and asserts that a Phase 3 trial of this size for mRNA-1273 "cannot produce an adequate safety profile" for the vaccine. Amended CP at 7. Petitioner asserts that, because the percentage of the population that suffers "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 mRNA-1273 vaccine. Amended CP at 8.

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 mRNA-1273 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 mRNA-1273 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" (Amended CP at 8), 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

[56] Moderna COVID-19 Vaccine EUA Letter of Authorization at 6.
[57] Id.
[58] Id. at 7.

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.[59] 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.[60] Petitioner asserts that "only 15,000 individuals" will be in the placebo and active vaccine arms of the study. Amended CP at 7. However, we note that sample sizes of 15,000 subjects in each 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 15,000 subjects per group (87% 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 Trials.[61] 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 provides a quotation from a May 24, 2020 CNN interview with Dr. Paul Offit,[62] and further asserts that

> 20,000 subjects in the group receiving the experimental vaccine, and certainly 15,000 subjects, will not be sufficient according to the a [sic] report from the Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, FDA, with regard to assessing the safety of mRNA-1273 for anyone other than the groups with the highest risk of complications from SARS-CoV-2.

Amended CP at 8. Petitioner cites to the publication Safety Considerations for New Vaccine Development by Susan S. Ellenberg.[63]

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[59] June 2020 Guidance at 15.
[60] Id.
[61] E9 Statistical Principles for Clinical Trials; Guidance for Industry, September 1998, https://www.fda.gov/media/71336/download
[62] Dr. Offit is a member of FDA's VRBPAC and is also the Director of the Vaccine Education Center at the Children's Hospital of Philadelphia, as well as the Maurice R. Hilleman Professor of Vaccinology and a Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania. Dr. Offit is quoted as saying "we are waiting for the big trial … the large prospective placebo controlled trial, we have 20,000 people who get a vaccine, 10,000 people who get a placebo, then and only then will you know whether a vaccine is safe and effective." Amended CP at 8. Notably, the quoted statement does not say that a clinical trial with 30,000 participants, such as that for mRNA-1273, is inadequate to assess safety and/or support authorization or licensure. The statement attributed to Dr. Offit seems to contemplate a clinical trial with 30,000 participants, but instead of 1:1 randomization such a trial would assign two thirds of study participants to the vaccine arm and one third to the placebo arm. However, the quoted statement does not assert that 1:1 randomization would be improper.
[63] Ellenberg, S., Safety considerations for new vaccine development, Pharmacoepidemiology and Drug Safety, 10: 411-415, 2001, https://pubmed.ncbi.nlm.nih.gov/11802587/.

Contrary to Petitioner's suggestion, the 2001 Ellenberg publication predates COVID-19 and addresses neither the mRNA-1273 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 mRNA-1273 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" (Amended CP at 8), 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.

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 child having a SARS-CoV-2 infection." Amended CP at 2, fn. 5. 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.[64] 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

[64] 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." Amended CP at 7-8. 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 September 17, 2020, https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/children/symptoms.html.

in protecting humans from SARS-CoV-2 infection and/or clinical disease.[65] 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.[66] The safety of vaccines such as mRNA-1273 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.[67] As noted above, a protocol of 15,000 subjects in each 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 mRNA-1273 clinical study was of sufficient size and adequately powered to support an EUA for the populations specified in the Moderna COVID-19 Vaccine EUA Letter of Authorization.

Because Petitioner has not supported the requests related to the size of the mRNA-1273 clinical study, FDA denies the requests.

3. T-Cell Reactivity

Petitioner requests that "the study design for the Phase III trial of mRNA-1273 SARS-CoV-2…be amended to provide that…participants are tested for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination." Amended 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."[68,69] Amended CP at 8.

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[65] June 2020 Guidance at 2.

[66] 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 as well as 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.

[67] FDA Moderna COVID-19 Vaccine Briefing Document.

[68] Sette, A., 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.

[69] 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

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."[70] 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.[71] 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.[72]

For the foregoing reasons, FDA denies Petitioner's request to require Moderna to conduct such testing in the mRNA-1273 clinical study.

C. The Petition for Stay of Action

In the PSA, Petitioner requests that FDA "[s]tay the Phase III trial of mRNA-1273 (NCT04470427) until its study design is amended" to provide that:

> a. any and all adverse events and reactions[] will be documented for the entire duration of the trial;
>
> b. such documenting of adverse events and reactions shall last at least twelve months for adults, thirty-six months for children, and sixty months for infants and toddlers;
>
> 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;[] and
>
> d. participants are tested for T-cell reactivity to SARS-CoV-2 pre-vaccination and post-vaccination.

PSA at 2.

> 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.

[70] Id. at 457–458.

[71] FDA Moderna COVID-19 Vaccine Briefing Document.

[72] 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.

1. Criteria for Granting an Administrative Stay of Action

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

> The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action as is warranted by the petition…The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:
>
> (1) The petitioner will otherwise suffer irreparable injury.
>
> (2) The petitioner's case is not frivolous and is being pursued in good faith.
>
> (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
>
> (4) The delay resulting from the stay is not outweighted by public health or other public interests.[73]

This section also contains a provision for the discretionary implementation of a stay in any proceeding if it is in the public interest and in the interest of justice.[74]

As stated in the regulation, the Commissioner shall grant a stay if all four of the criteria in 21 CFR § 10.35(e) apply. As explained below, we find that Petitioner has failed to demonstrate three of the four criteria in section 10.35(e). Consequently, we need not address Petitioner's assertion that the PSA is not frivolous and is being pursued in good faith. FDA also has the discretion to grant a stay if it is in the public interest and in the interest of justice to do so. We also decline to grant the PSA on the basis that Petitioner has not established that a stay would be in the public interest or the interest of justice.[75]

a. Petitioner Has Not Demonstrated Irreparable Injury

Petitioner contends that a stay must be granted because Petitioner will otherwise suffer irreparable injury. Petitioner's argument is that "once the FDA licenses this COVID-19 vaccine, states are expected to make this product mandatory, and hence without the FDA assuring proper safety trials of the vaccine *now*, the Petitioner will not have the opportunity to object to receiving the vaccine based on deficient clinical trials *later*." PSA at 3 and 8. Petitioner also asserts that "if the vaccine is licensed without an appropriate safety review, ethical considerations prevent

[73] 21 CFR § 10.35(e).
[74] See 21 CFR § 10.35(e).
[75] Petitioner states that "[t]he Petitioner hereby incorporates by reference as if fully set forth herein the Statement of Grounds from its Amended Citizen's Petition, dated July 20, 2020." PSA at 2, fn. 5. In that petition, the Action Requested relates to "Phase II and Phase III trials of COVID-19 vaccines." July 20, 2020 Amended Citizen Petition (Docket Number FDA-2020-P-1601), at 1. Although that petition does not specifically address the mRNA-1273 vaccine trial addressed here, we have considered the assertions in that petition for purposes of this response. We have responded to the July 20, 2020 Amended Citizen Petition and related submissions (contained in Docket Number FDA-2020-P-1601) separately.

conducting another placebo-controlled study post-licensure, thereby preventing any properly designed clinical trial from ever occurring." PSA at 3.

Petitioner's claim of injury is too remote. Petitioner asserts that it will be forced to receive an inadequately vetted vaccine due to State-level mandatory vaccination requirements. However, the PSA does not seek a stay of any FDA decision that will force any individuals to receive a vaccine (nor has the Agency imposed a vaccination requirement). Petitioner seeks a stay of the mRNA-1273 Phase 3 clinical trial but has not demonstrated that the continuation of the trial will cause States to issue requirements that will in turn cause Petitioner to be vaccinated against Petitioner's will. Indeed, there are numerous regulatory steps between the conduct of clinical trials and the existence of a vaccine that is available to the public – much less before any State or professional body makes any potential decisions regarding mandatory vaccination.[76] The continuation of the clinical trial, alone, will not cause the asserted harm. Furthermore, for the reasons stated above, Petitioner has not demonstrated any safety inadequacies that undercut FDA's decision to authorize the vaccine.[77]

Thus, Petitioner has not demonstrated that the continuation of the mRNA-1273 clinical trial will cause irreparable injury.

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

Petitioner asserts that the request is "supported by the sound public policy of assuring the safety of this product, to the greatest extent possible, before being injected into hundreds of millions of Americans." PSA at 3.

We do not agree that Petitioner has demonstrated sound public policy grounds supporting a stay. Petitioner seeks a stay of the mRNA-1273 Phase 3 clinical trial. 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)). FDA's implementing regulations in 21 CFR § 312.42 identify the circumstances that may justify a clinical hold. Although the mechanism by which FDA may "stay" a clinical trial is to issue a clinical hold, Petitioner has not identified any basis under 21 CFR § 312.42 or section 505(i)(3) of the FD&C Act for the mRNA-1273 clinical trial that would justify a clinical hold.

We conclude that a stay of a clinical trial is warranted only when a basis has been demonstrated for a clinical hold in accordance with 21 CFR § 312.42 and section 505(i)(3) of the FD&C Act. Because Petitioner has not identified any such basis, we disagree that Petitioner has

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

[77] The PSA appears to reflect a misunderstanding of the safety-related procedures in the mRNA-1273 clinical trial by asserting that "beyond these extremely short safety review periods, adverse events will only be captured if it results in the study participant withdrawing from the study." PSA at 4. Petitioner also states that "there are many autoimmune, neurological, and chronic health disorders which have a major impact on the quality of life that this vaccine could cause which would be ignored simply because the participant did not withdraw from the study." Id. As noted, the publicly-available mRNA-1273 protocol includes monitoring for certain adverse events for two years and is not limited to situations in which the study participant withdraws from the study. The protocol calls for including in safety assessments medically attended adverse events and serious adverse events from Day 1 through Day 759. See FDA Moderna COVID-19 Vaccine Briefing Document at 16.

demonstrated sound public policy grounds supporting the requested stay. We note that if FDA becomes aware of circumstances justifying a clinical hold, FDA may order a clinical hold in accordance with 21 CFR § 312.42 and section 505(i)(3) of the FD&C Act. In addition, for the reasons stated above, we do not agree that Petitioner has demonstrated deficiencies with the safety assessment procedures in the clinical trial.

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

Finally, Petitioner asserts that any delay caused by the requested stay is not outweighed by the public health or other public interests. In support of this argument, Petitioner states that "the public interest also weighs strongly in favor of the requested relief because having adequate safety review protocols will comport with the best interests of all Americans slated to receive this product and will increase public confidence in the safety and efficacy of this product." PSA at 3 and 9.

We conclude that Petitioner has not demonstrated that delay would be not be outweighed by public health or other public interests.

First and foremost, as is the case with all licensed or authorized vaccines, the mRNA-1273 vaccine to prevent COVID-19 is being authorized based on FDA's science-based decision-making process to assure our standards for safety and effectiveness are met.[78]

In addition, the extraordinary current public health situation further argues against any unnecessary delay in the timely development of a COVID-19 vaccine that meets all relevant regulatory requirements. This is especially true when Petitioner has not identified a single basis for FDA to stay (or place on hold) the mRNA-1273 clinical trial.[79]

In short, the public health and public interest in adequate and well-controlled clinical trials for COVID-19 vaccines is strong. We conclude that staying clinical trials without justification would not be in the public health or public interest, and Petitioner has not set forth any justification under our regulations for staying the mRNA-1273 clinical trial. The interests of public health would not be served if a stay interfered with the conduct of clinical trials without justification. In addition, for the reasons stated above, Petitioner has not demonstrated any safety inadequacies that undercut FDA's decision to authorize the vaccine.

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

Section 10.35 also provides that FDA may grant a stay of administrative action if the Agency believes it is in the public interest and in the interest of justice. As discussed above, we do not agree that a stay is in the public interest or the interest of justice at this time. It is in the public interest and the interest of justice to ensure that the clinical trial for the mRNA-1273 COVID-19 vaccine continues. Stays (or clinical holds) are only justified when there is a basis to do so under 21 CFR § 312.42 and section 505(i)(3) of the FD&C Act. It is not in the public interest or the interest of justice to stay clinical trials in response to petitions to the Agency that fail to

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

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

demonstrate any justification under 21 CFR § 312.42 and section 505(i)(3) of the FD&C Act for a clinical hold.

For the foregoing reasons, the PSA is denied.

IV. Conclusion

FDA has considered Petitioner's requests relating to the study of the mRNA-1273 vaccine to prevent COVID-19. For the reasons given in this letter, FDA denies the requests in Petitioner's citizen petitions and also denies the requests in the PSA. Therefore, we deny the Petitions in their entirety.

Sincerely,

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

cc: Dockets Management Staff

Appendix I: Aspects of Vaccine Development and Process for Licensure

A. Vaccines are Biologics and Drugs

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

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

B. Clinical Investigations of Vaccines

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

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

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

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

C. Biologics License Applications

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

Under § 601.2(a), FDA may approve a manufacturer's application for a biologics license only after the manufacturer submits an application accompanied by, among other things, "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency." The BLA must provide the multidisciplinary FDA reviewer team (medical officers, microbiologists, chemists, biostatisticians, etc.) with the Chemistry, Manufacturing, and Controls (CMC)[80] 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.

[80] 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.