



August 23, 2021

Meryl Nass, M.D.
Robert F. Kennedy, Jr.
Children's Health Defense
1227 North Peachtree Parkway
Suite 202
Peachtree City, GA 30269

Re: Citizen Petition (Docket Number FDA-2021-P-0460)

Dear Dr. Nass and Mr. Kennedy,

This letter responds to the citizen petition dated May 16, 2021 that you submitted to the Food and Drug Administration (FDA, the Agency, we) on behalf of Children's Health Defense (Petitioner) relating to: clinical trials, Emergency Use Authorization, licensure, and advertising and promotion of vaccines to prevent Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (the Petition).

In the Petition, Petitioner requests that FDA:

1. "revoke all EUAs and refrain from approving any future EUA, NDA, or BLA for any COVID vaccine for all demographic groups";
2. "immediately refrain from allowing minors to participate in COVID vaccine trials, refrain from amending EUAs to include children, and immediately revoke all EUAs that permit vaccination of children under 16 for the Pfizer vaccine and under 18 for other COVID vaccines";
3. "immediately revoke tacit approval that pregnant women may receive any EUA or licensed COVID vaccines and immediately issue public guidance to that effect";
4. "immediately amend [FDA's] existing guidance for the use of the chloroquine drugs, ivermectin, and any other drugs demonstrated to be safe and effective against COVID...and immediately issue notifications to all stakeholders";
5. "issue guidance to the Secretary of the Defense [sic] and the President not to grant an unprecedented Presidential waiver of prior consent regarding COVID vaccines for Servicemembers [sic]";
6. "issue guidance...to affirm that all citizens have the option to accept or refuse administration of investigational COVID vaccines without adverse work, educational or other non-health related consequences"; and

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

7. “[p]ending revocation of COVID vaccine EUAs, FDA should issue guidance that all marketing and promotion of COVID vaccines must refrain from labeling them ‘safe and effective.’”

Petition at 1-2.

In this letter, we discuss the safety of licensed and authorized vaccines. We then turn to the requests contained in the Petition. We consider each of your requests in light of the legal standards for FDA action, and provide our conclusions based on the facts, the science, and the law.

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

Here is an outline of our response:

- I. Background
- II. Vaccines That Are FDA-Licensed or Receive an Emergency Use Authorization Meet Relevant Statutory Requirements
 - a. Vaccines that are FDA-Licensed are Safe
 - i. Vaccines that are FDA-Licensed are Shown to Be Safe at the Time of Licensure
 - ii. Vaccine Safety Continues to Be Monitored Post-Licensure
 - b. An Emergency Use Authorization for a COVID-19 Preventative Vaccine Is Issued Only If the Relevant Statutory Standards Are Met
- III. Discussion
 - a. Investigational New Drugs
 - b. The Citizen Petition
 - i. Petitioner’s Request to Revoke all Emergency Use Authorizations for COVID-19 Vaccines and Refrain from Issuing any Future EUA or Approving any Future NDA, or BLA for any COVID-19 Vaccine for all Demographic Groups because the Current Risks of Serious Adverse Events or Deaths Outweigh the Benefits, and Because Existing, Approved Drugs Provide Highly Effective Prophylaxis and Treatment against COVID-19, Mooting the EUAs
 1. Petitioner’s Request to Revoke all Emergency Use Authorizations for COVID-19 Vaccines
 2. Petitioner’s Request to Refrain from Granting any Future EUA for a COVID-19 Vaccine for any Population
 3. Petitioner’s Request to Refrain from Approving any Future NDA for any COVID-19 Vaccine for any Population

4. Petitioner's Request to Refrain from Licensing any Future BLA for any COVID-19 Vaccine for any Population
- ii. Petitioner's Request Regarding COVID-19 Vaccines in Children
 1. Request to Immediately Refrain from Allowing COVID-19 Vaccine Trials to Include Pediatric Subjects
 2. Request that FDA Refrain from Issuing EUA Amendments for Authorized COVID-19 Vaccines to Include Indications for Pediatric Populations
 3. Request that FDA Immediately Revoke all EUAs for COVID-19 Vaccines with Pediatric Indications
- iii. Petitioner's Request that FDA Immediately Revoke Tacit Approval that Pregnant Women may Receive any EUA or Licensed COVID-19 Vaccines and Immediately Issue Public Guidance
 1. Covid-19 in Pregnancy
 2. Certain Content and Format Requirements for Prescription Drug Labeling for Products Approved Under NDAs or BLAs
 3. Inclusion of Contraindications and Pregnancy Information in the Labeling for the Authorized COVID-19 Vaccines
 4. Inclusion of Contraindications and Pregnancy Information in the Labeling for Licensed COVID-19 Vaccines
- iv. Petitioner's Request that FDA Immediately Amend its Guidance regarding Certain Approved Drugs [chloroquine drugs, ivermectin, "and any other drugs demonstrated to be safe and effective against COVID"]
- v. Petitioner's Request that FDA Issue Guidance to the Secretary of Defense and the President
- vi. Petitioner's Request that FDA Issue Guidance to Stakeholders Regarding the Option to Refuse or Accept Administration of Investigational COVID-19 Vaccines
- vii. Petitioner's Request that FDA Issue Guidance Regarding Marketing and Promotion of COVID-19 Vaccines

c. Conclusion

Appendix I: Aspects of Vaccine Development and Process for Licensure

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 Department of Health and Human Services (HHS) issued a declaration

of a public health emergency related to COVID-19.¹ On February 4, 2020, pursuant to section 564 of the FD&C Act (21 U.S.C. § 360bbb-3), 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-19.² On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (“COVID-19 EUA Declaration”), pursuant to section 564(b)(1) of the FD&C Act.³ In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.⁴

Commercial vaccine manufacturers and other entities are developing COVID-19 vaccine candidates, and clinical studies of these vaccines are underway and/or have been completed. Between December 11, 2020 and February 27, 2021, FDA issued emergency use authorizations for three vaccines to prevent COVID-19, including vaccines sponsored by Pfizer Inc. (Pfizer); ModernaTX, Inc. (Moderna); and Janssen Biotech, Inc. (Janssen), a pharmaceutical company of Johnson & Johnson. FDA received a Biologics License Application (BLA) for the COVID-19 vaccine, BNT162b2, intended to prevent COVID-19 in individuals 16 years of age and older. As announced by FDA on August 23, 2021, the Agency is issuing a biologics license for this COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) to BioNTech Manufacturing GmbH.⁵

II. Vaccines That Are FDA-Licensed or Receive an Emergency Use Authorization Meet Relevant Statutory Requirements

a. Vaccines that are FDA-Licensed are Safe

i. Vaccines that are FDA-Licensed Are Shown to Be Safe at the Time of Licensure

FDA has a stringent regulatory process for licensing vaccines.^{6,7} The Public Health Service Act (PHS Act) authorizes FDA to license biological products, including vaccines, if they have

¹ Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Originally issued on Jan. 31, 2020, and subsequently renewed),

<https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>

² HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020,

<https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency>.

³ HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020,

<https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration>.

⁴ Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak, issued March 13, 2020, <https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>.

⁵ BioNTech Manufacturing GmbH is the biologics license holder for this vaccine, which is manufactured by Pfizer Inc. for BioNTech Manufacturing GmbH (hereinafter “BioNTech”). The basis for FDA's licensure decision is set forth in FDA's Summary Basis for Regulatory Action (SBRA) for the BioNTech application. This memorandum will be posted on [fda.gov](https://www.fda.gov). We incorporate by reference the SBRA for the BLA.

⁶ 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>.

⁷ FDA, Vaccine Safety Questions and Answers, last updated March 2018, <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers>.

been demonstrated to be “safe, pure, and potent.”⁸ 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 biologics license application (BLA) 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.⁹

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.¹⁰ 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.”¹¹ Therefore, the manufacturers of vaccines that have been licensed in the U.S. have necessarily demonstrated the safety of the vaccines within the meaning of the applicable statutory and regulatory provisions before the vaccines were licensed and allowed to be marketed.

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

ii. 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.

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

Congress established the Emergency Use Authorization (EUA) pathway to ensure that, during public health emergencies, potentially lifesaving medical products could be made available before being approved. The EUA process allows the Secretary of HHS, in appropriate circumstances, to declare that EUAs are justified for products to respond to certain types of

⁸ 42 U.S.C. § 262(a)(2)(C)(i)(I).

⁹ 21 CFR § 601.2(a).

¹⁰ FDA, Vaccines, last updated January 2021, <https://www.fda.gov/vaccines-blood-biologics/vaccines>.

¹¹ 21 CFR § 601.2(d) (emphasis added).

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 United States (U.S.) citizens living abroad, and that involves the virus that causes COVID-19.¹² 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)).¹³

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

- The agent referred to in the March 27, 2020 EUA declaration by the Secretary (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

Although EUAs are governed under a different statutory framework than 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

¹² HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, <https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency>.

¹³ HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, <https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration>.

that would support issuance of an EUA for a vaccine to prevent COVID-19.¹⁴ 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.¹⁵ 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.¹⁶

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.¹⁷ During the entire study, subjects will be monitored for safety events. If the evidence from the clinical trial meets the pre-specified criteria for success for efficacy and the safety profile is acceptable, the results from the trial can potentially be submitted to FDA in support of an EUA request.

Investigational COVID-19 vaccines continue to be studied 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. 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.¹⁸ Furthermore, robust safety monitoring is conducted after a vaccine is made available. The monitoring systems include the

¹⁴ Emergency Use Authorization for Vaccines to Prevent COVID-19; Guidance for Industry, October 2020 (October 2020 Guidance), <https://www.fda.gov/media/142749/download>.

¹⁵ Id. at 3.

¹⁶ Id. at 4.

¹⁷ Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry, June 2020, <https://www.fda.gov/media/139638/download>.

¹⁸ October 2020 Guidance at 10-11.

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 Petition makes a request regarding clinical trials of COVID-19 vaccines that include or propose to include children. FDA’s investigational new drug process applies to the development of new drugs and biological products, including vaccines.¹⁹

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 studies²⁰) 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.²¹ The IND describes the proposed clinical study in detail and, among other things, helps protect the safety and rights of human subjects.²² 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

¹⁹ See 21 CFR § 312.2 (explaining that the IND regulations apply to clinical investigations of both drugs and biologics).

²⁰ 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.

²¹ See 21 CFR § 312.20(a).

²² 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>.

includes commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB),²³ 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.²⁴

FDA's regulations provide that, once an IND is in effect, the sponsor may conduct a clinical investigation of the product, with the investigation generally being divided into three phases. With respect to vaccines, the initial human studies, referred to as Phase 1 studies, are generally safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase 2 studies may include up to several hundred individuals and are designed to provide information regarding the incidence of common short-term side effects such as redness and swelling at the injection site or fever and to further describe the immune response to the investigational vaccine. If an investigational new vaccine progresses past Phase 1 and Phase 2 studies, it may progress to Phase 3 studies. For Phase 3 studies, the sample size is often determined by the number of subjects required to establish the effectiveness of the new vaccine, which may be in the thousands or tens of thousands of subjects. Phase 3 studies provide the critical documentation of effectiveness and important additional safety data required for licensing.

Additionally, FDA regulations require that an IRB must review clinical investigations involving children as subjects covered by 21 CFR 50, subpart D and only approve those clinical investigations involving children as subjects that satisfy the criteria in 21 CFR 50, subpart D, Additional Safeguards for Children in Clinical Investigations. As explained in the preamble to the final rule, "[t]hese safeguards are intended to ensure that the rights and welfare of children who participate in clinical investigations are adequately protected."²⁵

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

²³ 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>.

²⁴ 21 CFR § 312.22(a).

²⁵ Preamble to final rule, "Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products" (78 FR 12937 at 12938, February 26, 2013), <https://www.federalregister.gov/documents/2013/02/26/2013-04387/additional-safeguards-for-children-in-clinical-investigations-of-food-and-drug>.

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.²⁶

b. The Citizen Petition

i. Petitioner’s Request to Revoke all Emergency Use Authorizations for COVID-19 Vaccines and Refrain from Issuing any Future EUA or Approving any Future NDA, or BLA for any COVID-19 Vaccine for all Demographic Groups because the Current Risks of Serious Adverse Events or Deaths Outweigh the Benefits, and Because Existing, Approved Drugs Provide Highly Effective Prophylaxis and Treatment against COVID-19, Mooting the EUAs

Petitioner makes several requests regarding COVID-19 vaccines in the Petition and, in support of these requests, argues that (1) the rates of serious adverse events or deaths outweigh the benefits of these vaccines and (2) approved drugs provide highly effective prophylaxis/treatment against COVID, thereby “mooting” the EUAs. We interpret this as an argument that the authorizations of COVID-19 vaccines to date did not meet the relevant legal standard. Below, we address each of Petitioner’s requests and the information provided by Petitioner in support of these requests.

1. Petitioner’s Request to Revoke all Emergency Use Authorizations for COVID-19 Vaccines

In this section, we address Petitioner’s request that FDA “revoke all EUAs . . . for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs.” Petition at 1.

a. EUAs for COVID-19 Vaccines

As noted above in Section II above, FDA may issue an EUA during the COVID-19 public health emergency after FDA concludes that the statutory requirements provided in section 564 of the FD&C Act are met. In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates have been developed. COVID-19 vaccines that have been developed or are currently in development are based on various platforms and include mRNA, DNA, viral vectored, subunit, inactivated, and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain, as the immunogenic determinant.

To date, FDA has issued EUAs for three COVID-19 vaccines (“the Authorized COVID-19 Vaccines”), as described in the Scope of Authorization for these COVID-19 vaccines, pursuant

²⁶ 21 CFR § 312.42(a).

to section 564 of the FD&C Act. Additionally, FDA has expanded the authorized age range for one COVID-19 vaccine.

- On December 11, 2020, FDA issued an EUA for emergency use of Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age and older.
 - On May 10, 2021, FDA authorized the emergency use of Pfizer-BioNTech COVID-19 Vaccine to include individuals 12 through 15 years of age.
- On December 18, 2020, FDA issued an EUA for emergency use of Moderna COVID-19 Vaccine for the prevention of COVID-19 in individuals 18 years of age and older.
- On February 27, 2021, FDA issued an EUA for emergency use of Janssen COVID-19 Vaccine for the prevention of COVID-19 in individuals 18 years of age and older.

The Agency issued these EUAs after a thorough evaluation of scientific data regarding the safety, effectiveness, and manufacturing information (which helps ensure product quality and consistency) of these COVID-19 vaccines and after reaching a determination that these vaccines meet the statutory requirements under section 564 of the FD&C Act. This letter incorporates by reference the EUA Review Memoranda for the Authorized COVID-19 Vaccines,²⁷ which discuss this determination, and the data upon which it was based, in detail as well as the Summary Basis of Regulatory Action for the BioNTech COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty).²⁸

Petitioner argues that the authorizations for these vaccines should be revoked, and that future COVID vaccines should not be authorized or licensed, because (1) “the current risks of serious adverse events or deaths outweigh the benefits,” and (2) “existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooted the EUAs.” We address each of Petitioner’s arguments, and data submitted in the Petition in support of these arguments, below.

FDA disagrees with Petitioner’s position that the Authorized COVID-19 Vaccines did not meet the statutory standard at the time of authorization, and finds no basis in the information submitted in the Petition, or in any postmarket data regarding these vaccines, to support a revocation of any of these authorizations. FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. The

²⁷ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), <https://www.fda.gov/media/144416/download>; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), <https://www.fda.gov/media/148542/download>; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021) <https://www.fda.gov/media/151613/download>; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), <https://www.fda.gov/media/144673/download>; FDA, Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021) <https://www.fda.gov/media/151611/download>; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), <https://www.fda.gov/media/146338/download>.

²⁸ This letter incorporates by reference FDA’s Summary Basis for Regulatory Action (SBRA) for the BioNTech BLA. This memorandum will be posted on www.fda.gov.

known and potential benefits of the Authorized COVID-19 Vaccines continue to outweigh their known and potential risks, given the risk of COVID-19 and related, potentially severe, complications. Furthermore, as explained below, there is no adequate, approved, and available alternative to the Authorized COVID-19 Vaccines for preventing COVID-19. Accordingly, this request is denied.

b. Standard for Revocation of EUAs is not Met for the Authorized COVID-19 Vaccines

Section 564(g)(2) of the FD&C Act provides the standard for revocation of an EUA. Under this statutory authority, FDA may revise or revoke an EUA if:

- (A) the circumstances described under [section 564(b)(1) of the FD&C Act] no longer exist;
- (B) the criteria under [section 564(c) of the FD&C Act] for issuance of such authorization are no longer met; or
- (C) other circumstances make such revision or revocation appropriate to protect the public health or safety.

FDA's guidance entitled *Emergency Use Authorization of Medical Products and Related Authorities* ("EUA Guidance"),²⁹ notes that once an EUA is issued for a product, in general, that EUA will remain in effect for the duration of the EUA declaration under which it was issued, "unless the EUA is revoked because the criteria for issuance . . . are no longer met or revocation is appropriate to protect public health or safety (section 564(f),(g) [of the FD&C Act])."³⁰ Regarding the circumstances that would make a revision or revocation appropriate to protect the public health or safety, FDA explains in the EUA guidance that

Such circumstances may include significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.

²⁹ Emergency Use Authorization of Medical Products and Related Authorities; Guidance for Industry and Other Stakeholders, January 2017 (EUA Guidance), <https://www.fda.gov/media/97321/download>.

³⁰ Id. at 28.

EUA guidance at 29.

Thus, in addressing Petitioner’s request for FDA to revoke the Authorized COVID-19 Vaccines, we assess whether any of the statutory conditions under which FDA may revoke an EUA are met, namely: (1) whether the circumstances justifying their issuance under section 564(b)(1) of the FD&C Act no longer exist, (2) whether the criteria for their issuance under section 564(c) of the FD&C Act are no longer met, and (3) whether other circumstances make a revision or revocation appropriate to protect the public health or safety.

i. Circumstances Continue to Justify the Issuance of the EUAs for the Authorized COVID-19 Vaccines

As explained above in section II.b., 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-19.³¹ On the basis of such determination, on March 27, 2020, the Secretary then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (“COVID-19 EUA Declaration”), pursuant to section 564(b)(1) of the FD&C Act (21 U.S.C. § 360bbb-3(b)(1)).³²

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 statutory requirements provided in section 564(c) are met. Section 564(b)(2) sets forth the statutory standard for termination of an EUA declaration. An EUA declaration remains in place until the earlier of: (1) a determination by the HHS Secretary that the circumstances that precipitated the declaration have ceased (after consultation as appropriate with the Secretary of Defense) or (2) a change in the approval status of the product such that the authorized use(s) of the product are no longer unapproved. Neither of those statutory criteria is satisfied with respect to the Authorized COVID-19 Vaccines.

Thus, the circumstances described under section 564(b)(1) of the FD&C Act continue to exist. FDA therefore is not revoking the EUAs for the Authorized COVID-19 Vaccines under the authority in section 564(g)(2)(A) of the FD&C Act.

ii. The Criteria for The Issuance of the Authorized COVID-19 Vaccines Continue to Be Met

This section describes in detail why the criteria under section 564(c) of the FD&C Act continue to be met with respect to the Authorized COVID-19 Vaccines and why, therefore, FDA is not revoking the EUAs for the Authorized COVID-19 Vaccines under the authority in section 564(g)(2)(B) of the FD&C Act.

³¹ HHS, Determination of Public Health Emergency, 85 FR 7316, February 7, 2020, <https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency>.

³² HHS, Emergency Use Authorization Declaration, 85 FR 18250, April 1, 2020, <https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration>.

1. Serious or life-threatening disease or condition.

Section 564(c)(1) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude “the agent(s) referred to in [the HHS Secretary’s EUA declaration] can cause a serious or life-threatening disease or condition.” FDA has concluded that SARS-CoV-2, which is the subject of the EUA declaration, meets this standard.

The SARS-CoV-2 pandemic continues to present an extraordinary challenge to global health and, as of August 3, 2021, has caused more than 199 million cases of COVID-19 and claimed the lives of more than 4.2 million people worldwide.³³ In the United States, more than 34 million cases and over 611,000 deaths have been reported to the CDC.³⁴ On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS, and the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020.

FDA is not aware of science indicating that there is any change in the ability of the SARS-CoV-2 virus to cause a serious or life-threatening disease or condition, namely COVID-19, nor has Petitioner provided any information about such a change. Therefore, the criterion under section 564(c)(1) continues to be met with respect to the Authorized COVID-19 Vaccines.

2. Evidence of Effectiveness

Section 564(c)(2)(A) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude “based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.”

FDA issued EUAs for the Authorized COVID-19 Vaccines after determining that, among other things, these products were demonstrated in clinical trials to prevent symptomatic and severe COVID-19 in vaccinated clinical trial subjects.³⁵ FDA is not aware of any data that changes this conclusion, nor has Petitioner provided any such data in the Petition. This section addresses Petitioner’s arguments regarding the effectiveness of the Authorized COVID-19 vaccines and explains why the information submitted by Petitioner does not change FDA’s analysis regarding the effectiveness of these vaccines.

After FDA approves a vaccine or authorizes a vaccine for emergency use, the vaccine continues to be studied to determine how well it works under real-world conditions. FDA, CDC, and other federal partners have been assessing, and will continue to assess, COVID-19 vaccine

³³ Johns Hopkins University School of Medicine, Coronavirus Resource Center, <https://coronavirus.jhu.edu/map.html>.

³⁴ CDC, COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases.

³⁵ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 23, <https://www.fda.gov/media/144416/download>; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 24, <https://www.fda.gov/media/144673/download>; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 25, <https://www.fda.gov/media/146338/download>.

effectiveness under real-world conditions. Such evaluations will help us understand if vaccines are performing as expected outside the more controlled setting of a clinical trial.

Petitioner raises concerns regarding the post-market effectiveness of the Authorized COVID-19 Vaccines (Petition at 6). Petitioner points to CDC-reported “breakthrough cases” to suggest that the Authorized COVID-19 Vaccines are not effective and argues that the EUAs for the Authorized COVID-19 Vaccines should therefore be revoked because the current risks of these vaccines outweigh their benefits. This perspective fails to recognize several important points regarding the concept of breakthrough cases and regarding the CDC publication cited in the Petition.

First, we note that the Letters of Authorization for the Authorized COVID-19 Vaccines require EUA-holders to report to VAERS “cases of COVID-19 that result in hospitalization or death, that are reported to [the EUA holder].”³⁶ Thus, the possibility that individuals who received one of the Authorized COVID-19 Vaccines could develop breakthrough COVID-19 cases was recognized by FDA when the Agency evaluated the EUA requests for these vaccines and determined that their known and potential benefits outweigh their known and potential and risks.

Second, the Authorized COVID-19 Vaccines are indicated to prevent *symptomatic* COVID-19,³⁷ not to prevent SARS-CoV-2 infection. Over 353 million doses of COVID-19 vaccines have been administered in the United States³⁸ and FDA’s ongoing post authorization monitoring informs us that the known and potential benefits continue to outweigh the known and potential risks. Additionally, CDC’s post-authorization data regarding the Authorized COVID-19 Vaccines continues to support FDA’s conclusion that these vaccines prevent *symptomatic* COVID-19.³⁹

Third, a vaccine does not need to be 100% effective in preventing the target disease in order to meet the licensure or EUA standard. It is expected that some vaccinated individuals will contract the target disease despite having been vaccinated against it. No FDA licensed or authorized vaccine is 100% effective, but scientific data has nevertheless demonstrated that vaccinations have been a very effective approach to protecting the public's health in the United States.⁴⁰

³⁶ Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Pfizer-BioNTech COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, <https://www.fda.gov/media/144413/download>; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Moderna COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, <https://www.fda.gov/media/144637/download>; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Janssen COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, <https://www.fda.gov/media/146304/download>.

³⁷ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 23, <https://www.fda.gov/media/144416/download>; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 24, <https://www.fda.gov/media/144673/download>; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 25, <https://www.fda.gov/media/146338/download>.

³⁸ CDC, COVID Data Tracker Weekly Review, Interpretive Summary for August 13, 2021, <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html>

³⁹ CDC, COVID-19 Vaccine Effectiveness Research, <https://www.cdc.gov/vaccines/covid-19/effectiveness-research/protocols.html>.

⁴⁰ Vaccine Safety Questions and Answers, last updated March 2018, <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers>.

Similarly, a COVID-19 vaccine need not be 100% effective in preventing symptomatic COVID-19, or even close to 100% effective in doing so, in order to have a significant effect in altering the course of the COVID-19 pandemic. As FDA noted in its June 2020 Guidance for Industry, Development and Licensure of Vaccines to Prevent COVID-19, (“The Vaccine Development and Licensure Guidance”) “[t]o ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%.”⁴¹ This statistical consideration provided in the Vaccine Development and Licensure Guidance reflects FDA’s assessment that a vaccine with at least 50 percent efficacy would have a significant impact on disease, both at the individual and societal level.

Finally, we note that Petitioner refers to “CDC-reported” breakthrough cases in support of its argument that there are effectiveness concerns with the Authorized COVID-19 Vaccines but fails to acknowledge that CDC reported a set of breakthrough cases that includes a large proportion of *asymptomatic* individuals who tested positive for SARS-CoV-2. Petitioner thus applies a narrower definition of the term “breakthrough case” to a set of cases than CDC has in its COVID-19 Vaccine Breakthrough Case Investigation.⁴² Petitioner refers to breakthrough cases in which vaccinated individuals “fall ill and potentially transmit the virus” (Petition at 6) and states that “CDC reported over 9,000 ‘breakthrough cases’ and 132 COVID-caused deaths among vaccinated people.” Petition at 6.

CDC’s objective in the COVID-19 Vaccine Breakthrough Case Investigation is to⁴³ ensure the COVID-19 vaccines are working as expected and to “identify patterns or trends” in:

- Patients’ characteristics, such as age or underlying medical conditions
- The specific vaccine that patients received
- Whether a specific SARS-CoV-2 variant caused the infections”⁴⁴

The objective of this investigation is not simply to count symptomatic COVID-19 cases. Currently, COVID-19 cases are increasing again in nearly all states. The highest rate of COVID-19 case spread is in areas with low vaccination rates.⁴⁵

Petitioner’s submitted data regarding CDC-reported “breakthrough cases” therefore does not present new data or information that the Agency has not previously considered regarding the effectiveness of the Authorized COVID-19 Vaccines. Available data regarding effectiveness of

⁴¹ Development and Licensure of Vaccines to Prevent COVID-19, Guidance for Industry, June 2020, at 14, <https://www.fda.gov/media/139638/download>.

⁴² CDC, COVID-19 Vaccine Breakthrough Case Investigations and Reporting, <https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html>.

⁴³ CDC, COVID-19 Vaccine Breakthrough Case Investigations and Reporting, <https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html>.

⁴⁴ CDC, COVID-19 Vaccine Breakthrough Case Investigations and Reporting, <https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html>.

⁴⁵ “As of July 22 [2021], 35% of U.S. counties are experiencing high levels of community transmission. COVID-19 cases are on the rise in nearly 90% of U.S. jurisdictions, and we are seeing outbreaks in parts of the country that have low vaccination coverage.” CDC, COVID Data Tracker Weekly Review, Interpretive Summary for July 23, 2021, available at <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html>.

the Authorized COVID-19 Vaccines continues to support the conclusion that these vaccines may be effective in preventing COVID-19. FDA is not aware of any data that changes this conclusion, nor has Petitioner provided any such data in the Petition. Therefore, the criterion under section 564(c)(2)(A) continues to be met with respect to the Authorized COVID-19 Vaccines.

3. Benefit-Risk Analysis

Section 564(c)(2)(B) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude “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” Petitioner argues that the current risks of serious adverse events or deaths associated with the Authorized COVID-19 Vaccines outweigh the benefits of COVID-19 vaccines. This section addresses Petitioner’s arguments regarding the safety of COVID-19 vaccines and explains why the information submitted by Petitioner does not change FDA’s analysis regarding the benefits and risks of the Authorized COVID-19 Vaccines.

FDA issued EUAs for the Authorized COVID-19 Vaccines after reaching a determination regarding each of these vaccines that, among other things, the known and potential benefits of the vaccine, when used to prevent COVID-19, outweigh its known and potential risks.⁴⁶ FDA is not aware of any data that changes this determination, nor has Petitioner provided any such data in the Petition. The known and potential benefits of the Authorized COVID-19 Vaccines, when used to prevent COVID-19, continue to outweigh their known and potential risks, given the risk of COVID-19 and related, potentially severe, complications.

Petitioner raises numerous concerns regarding safety of the Authorized COVID-19 Vaccines (Petition at 2-6) and asserts that the EUAs for the Authorized COVID-19 Vaccines should be revoked due in part to these safety concerns. For reasons explained below, FDA disagrees with Petitioner’s assertions regarding the safety of the Authorized COVID-19 Vaccines.

As an initial matter, we note that the Petition discusses several assertions made by CDC and requests that have been directed to CDC. For requests intended for CDC, you should contact CDC directly.

a. Petitioner’s Claims Regarding VAERS Data

⁴⁶ For an extensive discussion of FDA’s analysis of the clinical trial data regarding the risks and benefits of each of the authorized COVID-19 Vaccines, *see* FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 49, <https://www.fda.gov/media/144416/download>; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 55, <https://www.fda.gov/media/144673/download>; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 59, <https://www.fda.gov/media/146338/download>. *See also*, FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), at 38, <https://www.fda.gov/media/148542/download>.

In arguing that the Authorized COVID-19 Vaccines should be revoked due, in part, to safety concerns, Petitioners assert that “Vaccine Adverse Event Reporting System (VAERS) data reveal unprecedented levels of deaths and other adverse events since the FDA issued Emergency Use Authorizations (EUAs) for three COVID vaccines. As of May 10, 2021, VAERS reported 4,434 deaths of people who received at least one COVID vaccination.” As an initial matter, we note that VAERS is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed or authorized in the United States. VAERS is not designed to assess whether a reported adverse event was caused by a vaccine. This section explains vaccine safety surveillance, including VAERS, in greater detail below.

Regarding the number of VAERS reports submitted for the Authorized COVID-19 Vaccines, this figure can be attributed to multiple factors. First, we note that a large number of COVID-19 vaccine doses have been administered in the United States and that certain adverse event reporting by vaccination providers is *required* for the Authorized COVID-19 Vaccines. As of August 13, 2021, over 353,000,000 doses of the Authorized COVID-19 Vaccines have been administered.⁴⁷ We note that the crude number of VAERS reports of death is extremely small compared to the to the large number of people who have been vaccinated. The VAERS reporting rate for deaths (which is the number of VAERS death reports received out of the number of individuals vaccinated) for the Authorized COVID-19 Vaccines is actually very low (6,490 reports of death out of 346 million doses administered (0.0019%) as of August 2, 2021).⁴⁸ Petitioner’s assertion fails to account for this fact.

For licensed vaccines, healthcare providers are legally required under 42 USC 300aa-25 to report to VAERS two categories of adverse events: “[a]ny adverse event listed in the VAERS Table of Reportable Events Following Vaccination that occurs *within the specified time period after vaccination* [and] [a]n adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine”⁴⁹ Vaccine manufacturers are also required to report to VAERS all adverse events that come to their attention.⁵⁰

Under the EUAs for the Authorized COVID-19 Vaccines, however, vaccination providers are required to report to VAERS serious adverse events following vaccination with the Authorized COVID-19 Vaccines, “irrespective of attribution to vaccination” and without a specified time period after vaccination.⁵¹ Another contributing factor is the v-safe system,⁵² which is a new CDC smartphone-based active-surveillance system in which participants who have been

⁴⁷ CDC, COVID Data Tracker, COVID-19 Vaccinations in the United States, https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total.

⁴⁸ CDC, Selected Adverse Events Reported after COVID-19 Vaccination, <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html>.

⁴⁹ VAERS, Frequently Asked Questions, <https://vaers.hhs.gov/faq.html> (emphasis added).

⁵⁰ 21 CFR 600.80. See also VAERS, Frequently Asked Questions, <https://vaers.hhs.gov/faq.html>.

⁵¹ Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Pfizer-BioNTech COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, <https://www.fda.gov/media/144413/download>; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Moderna COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, <https://www.fda.gov/media/144637/download>; Section 8, Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors, Janssen COVID-19 Fact Sheet for Healthcare Providers Administering Vaccine, <https://www.fda.gov/media/146304/download>.

⁵² CDC, v-safe Overview, <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html>.

vaccinated may voluntarily enroll. This system was developed for the COVID-19 vaccination program. V-safe sends text messages and web surveys to participants who can report side effects following receipt of a COVID-19 vaccine. If a participant indicates through the v-safe surveys that he or she required medical care at any time, CDC calls the participant to complete a report through VAERS. This system is unique to COVID-19 vaccines and may be contributing to the number of VAERS reports submitted for the Authorized COVID-19 Vaccines. Finally, another potential factor is the concept of “stimulated reporting.”⁵³ Because of extensive media coverage and awareness of the public health emergency – and of the Authorized COVID-19 Vaccines and their reported side effects – vaccine recipients, health care providers, and others are more likely to report adverse events for the Authorized COVID-19 Vaccines than for other vaccines that have been widely available for longer periods of time. Additionally, one of the articles submitted by Petitioner in support of their argument actually provides support for this explanation for the number of VAERS reports submitted for the Authorized COVID-19 Vaccines. The article notes “[t]he relatively rapid increase in numbers of reports to VAERS following the introduction and initial uptake of a new vaccine, an expected occurrence, has been *misinterpreted as actual increases in incidence of adverse events and vaccine related risk.*”⁵⁴ Petitioner’s argument regarding VAERS data for the Authorized COVID-19 Vaccines is unavailing because it fails to account for the factors outlined above.

In addressing Petitioner’s assertion regarding VAERS claims, this section addresses the extensive vaccine safety surveillance efforts, in addition to VAERS, that are in place for the Authorized COVID-19 Vaccines.⁵⁵ FDA is monitoring the safety of the Authorized COVID-19 Vaccines through both passive and active safety surveillance systems. FDA is doing so in collaboration with the Centers for Disease Control and Prevention (CDC), the Centers for Medicare and Medicaid Services (CMS), the Department of Veterans Affairs (VA), and other academic and large non-government healthcare data systems.

In addition, FDA participates actively in ongoing international pharmacovigilance efforts, including those organized by the International Coalition of Medicines Regulatory Authorities

⁵³ We note that an article submitted by Petitioner in support of their arguments regarding VAERS acknowledges this concept: “Like all spontaneous public health reporting systems, VAERS has limitations. VAERS is subject to reporting bias, including underreporting of adverse events – especially common, mild ones– and stimulated reporting, which is elevated reporting that might occur in response to intense media attention and increased public awareness, such as during the 2009 H1N1 pandemic influenza vaccination program” Shimabukuro et al., Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), *Vaccine* (Nov. 4, 2015), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/>. See also “The number of reports and reporting rate following 2009-H1N1 vaccination were higher than following 2009–2010 seasonal influenza vaccines for all age groups. These findings, however, should be interpreted in light of the publicity around the 2009-H1N1 vaccine and efforts to increase reporting to VAERS. Heightened public awareness and stimulated reporting likely enhanced reporting to VAERS. Furthermore, although 2009-H1N1 was licensed similarly to seasonal influenza vaccines, it was likely perceived as a ‘new’ vaccine by the public and susceptible to the known tendency (i.e., the Weber effect) for adverse events to be reported more frequently following newly licensed products.” Vellozzi, et al., Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009–January 31, 2010, *Vaccine* (Oct. 21, 2010), <https://www.sciencedirect.com/science/article/pii/S0264410X10013319>.

⁵⁴ Shimabukuro et al., Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), *Vaccine* (Nov. 4, 2015), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/> (emphasis added).

⁵⁵ FDA, COVID-19 Vaccine Safety Surveillance, <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance>.

(ICMRA) and the World Health Organization (WHO). These efforts are in addition to the pharmacovigilance efforts being undertaken by the individual manufacturers for authorized vaccines. A coordinated and overlapping approach using state-of-the-art technologies has been implemented. As part of our efforts to be transparent about our COVID-19 vaccine safety monitoring activities, FDA is posting summaries of the key safety monitoring findings on the FDA website.⁵⁶

i. Vaccine Safety Surveillance

Passive Surveillance

VAERS is a national passive surveillance vaccine safety database that receives unconfirmed reports of possible adverse events following the use of a vaccine licensed or authorized in the United States. Passive surveillance is defined as unsolicited reports of adverse events that are sent to a central database or health authority. In the United States, these are received and entered into VAERS, which is co-managed by FDA and CDC. In the current pandemic, these reports are being used to monitor the occurrence of both known and unknown adverse events, as providers of COVID-19 vaccines are required to report serious adverse events to VAERS.

As part of FDA and CDC's multi-system approach to post-licensure and post-authorization vaccine safety monitoring, VAERS is designed to rapidly detect unusual or unexpected patterns of adverse events, also known as "safety signals." VAERS reports generally cannot be used to determine if a vaccine caused or contributed to an adverse event or illness. If the VAERS data suggest a possible link between an adverse event and vaccination, the relationship may be further studied in a controlled fashion.⁵⁷

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.

VAERS is not designed to assess causality. 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, we often receive 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, including COVID-19 vaccines, and a possible adverse event.

If VAERS monitoring suggests that a vaccine might be causing a health problem, additional scientifically rigorous studies or investigations can be performed by FDA and CDC. 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

⁵⁶ FDA, COVID-19 Vaccine Safety Surveillance, <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance>

⁵⁷ FDA, VAERS Overview, <https://www.fda.gov/vaccines-blood-biologics/vaccine-adverse-events/vaers-overview>.

understand possible biologic hypotheses that could plausibly link the reported adverse event to the vaccine. We review the pre-licensure or pre-authorization 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 (ACIP), and the Advisory Committee on Childhood Vaccines, and are often discussed with experts from other countries and from the World Health Organization. Federal agencies that assist in population-based vaccines safety studies include the CDC, 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.

Active Surveillance

Active surveillance involves proactively obtaining and rapidly analyzing information related to millions of individuals and recorded in large healthcare data systems to verify safety signals identified through passive surveillance or to detect additional safety signals that may not have been reported as adverse events to passive surveillance systems. FDA is conducting active surveillance using the Sentinel BEST (Biologics Effectiveness and Safety) System and the CMS system, and is also collaborating with other federal and non-federal partners.

BEST

To elaborate further, the BEST system,⁵⁸ which is part of the Sentinel initiative,⁵⁹ comprises large-scale claims data, electronic health records (EHR), and linked claims-EHR databases with a data lag of approximately three months. The system makes use of multiple data sources and enables rapid queries to detect or evaluate adverse events as well as studies to answer specific safety questions for vaccines. The linked claims-EHR database makes it possible to study the safety of vaccines in sub-populations with pre-existing conditions or in pregnant women. The major partners for BEST currently are Acumen, IBM Federal HealthCare, IQVIA, and Columbia University and many affiliated partners such as MedStar Health, BlueCross BlueShield of

⁵⁸ CBER Biologics Effectiveness and Safety (BEST) System, <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system>.

⁵⁹ FDA’s Sentinel Initiative, <https://www.fda.gov/safety/fdas-sentinel-initiative>.

America, the Observational Health Data Sciences and Informatics (OHDSI), OneFlorida, University of California and several others.⁶⁰

Using BEST, CBER plans to monitor about 15 adverse events⁶¹ that have been seen with the deployment of previous vaccines but have yet to be associated with a safety concern for an authorized COVID-19 vaccine at this time. CBER further plans to use the BEST system to conduct more in-depth analyses should a safety concern be identified from sources such as VAERS.

CMS

FDA has worked over the past several years with CMS to develop capabilities for routine and time-sensitive assessments of the safety of vaccines for people 65 years of age and older using the Medicare Claims database.⁶² Because it was already in place, this system was immediately put into use for COVID-19 vaccine surveillance to monitor for adverse events.⁶³

During the current pandemic, FDA, CMS, and CDC have already used the Medicare data to publish a study showing that frailty, comorbidities, and race/ethnicity were strong risk factors of COVID-19 hospitalization and death among the U.S. elderly.⁶⁴

VSD

In addition, the Vaccine Safety Datalink (VSD) is a collaborative project between CDC's Immunization Safety Office and nine health care organizations. As noted on the CDC's

⁶⁰ To confirm the utility of the BEST system for situations such as COVID-19 vaccine surveillance, a test case was conducted. This study aimed to replicate a previous study by the CDC's [Vaccine Safety Datalink](#) (VSD) (Klein et al. [Pediatrics 2010](#)) that examined the databases and analytic capabilities of the new system. The objective of this study was to test the new system's ability to reproduce the increased risk of febrile seizures in children receiving the first dose of measles-mumps-rubella-varicella (MMRV) vaccine, compared to that of MMR and varicella vaccines separately but on the same day. The results of the study met the objectives and demonstrated the ability of the BEST Initiative data network to run a complex study protocol at multiple sites using a distributed data network and the [Observational Medical Outcomes Partnership Common Data Model](#) (organizing disparate data sources into the same database design using a common format).

⁶¹ Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring, Draft Protocol (December 31, 2020), <https://www.bestinitiative.org/wp-content/uploads/2021/01/C19-Vaccine-Safety-AESI-Background-Rate-Protocol-2020.pdf>.

⁶² CMS, Standard Analytical Files (Medicare Claims) – LDS, <https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/StandardAnalyticalFiles>.

⁶³ As one example of the capabilities of this system, FDA, CMS, and CDC evaluated the risk of Guillain-Barré syndrome (GBS) following influenza vaccination after CDC's [Vaccine Safety Datalink](#), identified [safety signals](#) suggesting an increased risk of GBS following high-dose influenza vaccinations and Shingrix vaccinations during the 2018-2019 influenza season. CBER, CDC, and CMS formed working groups in February 2019 to refine these safety signals in the CMS data.

⁶⁴ Hector S Izurieta, David J Graham, Yixin Jiao, Mao Hu, Yun Lu, Yue Wu, Yoganand Chillarige, Michael Wernecke, Mikhail Menis, Douglas Pratt, Jeffrey Kelman, Richard Forshee, Natural History of Coronavirus Disease 2019: Risk Factors for Hospitalizations and Deaths Among >26 Million US Medicare Beneficiaries, *The Journal of Infectious Diseases*, Volume 223, Issue 6, 15 March 2021, Pages 945–956, <https://doi.org/10.1093/infdis/jiaa767> <https://academic.oup.com/jid/article/223/6/945/6039057>.

webpage, the VSD started in 1990 and continues today in order to monitor safety of vaccines and conduct studies about rare and serious adverse events following immunization.

The VSD uses electronic health data from each participating site. This includes information on vaccines: the kind of vaccine given to each patient, date of vaccination, and other vaccinations given on the same day. The VSD also uses information on medical illnesses that have been diagnosed at doctors' offices, urgent care visits, emergency department visits, and hospital stays. The VSD conducts vaccine safety studies based on questions or concerns raised from the medical literature and reports to the Vaccine Adverse Event Reporting System (VAERS). When there are new vaccines that have been recommended for use in the United States or if there are changes in how a vaccine is recommended, the VSD will monitor the safety of these vaccines.

The VSD has a long history of monitoring and evaluating the safety of vaccines. Since 1990, investigators from the VSD have published many studies to address vaccine safety concerns.⁶⁵

In summary, in collaboration and coordination with several different partners, FDA has assembled passive surveillance systems - including VAERS - and active surveillance systems that can detect and refine safety findings with the Authorized COVID-19 Vaccines in a relatively rapid manner. These systems can also potentially be leveraged to assess safety in specific subpopulations and to assess vaccine effectiveness.

ii. Articles Submitted in Petition Regarding Vaccine Surveillance

We note at the outset that Petitioner raises concerns regarding the methodology by which CDC calculated rates of anaphylactic adverse events post-vaccination. Such concerns are best directed to CDC and are outside the scope of FDA's Petition response.

Regarding Petitioner's contention that a low percentage of adverse events have been reported to VAERS and that therefore "the safety of COVID vaccines is considerably worse than it currently appears" (Petition at 4), as explained in detail above in this section, VAERS is only one part of a multi-tiered vaccine safety surveillance system, so the information derived from VAERS reports does not represent the full extent of vaccine safety information being monitored by FDA and its federal partners.

Specifically, Petitioner cites to three studies in support of the argument that "[g]iven that only 1 to 13% of adverse reactions have been reported to the FDA and CDC via the VAERS passive reporting system, according to Lazarus et al., the high number of adverse events and deaths following COVID vaccines is alarming." Petition at 5. The articles cited by Petitioner in support of this contention do not support Petitioner's position that, due to underreporting of adverse events, the rate of reported adverse events associated with COVID-19 vaccination is low in comparison to the actual rate of adverse events. As discussed above in this section, there are several factors unique to the surveillance of the Authorized COVID-19 Vaccines that have

⁶⁵ See, e.g., CDC, White Paper on the Safety of the Childhood Immunization Schedule, Vaccine Safety Datalink, available at https://www.cdc.gov/vaccinesafety/pdf/WhitePaperSafety_WEB.pdf.

contributed to the number of VAERS reports submitted for these vaccines. Petitioner’s argument that adverse events associated with the Authorized COVID-19 Vaccines are underreported because of the figures presented in the articles cited fail to account for any of those factors that are unique to the Authorized COVID-19 Vaccines.

Petitioner cites to a publication from the Agency for Healthcare Research and Quality (Lazarus et al.) in support of the argument that deaths and adverse events associated with the Authorized COVID-19 Vaccines are underreported because “only 1 to 13% of adverse reactions have been reported to the FDA and CDC via the VAERS passive reporting system” (Petition at 5), and therefore the actual rate of COVID-19 Vaccine adverse events is significantly higher than reported.⁶⁶ As an initial matter, we note that the language cited from the Lazarus article is referring to adverse event reporting for drugs and vaccines, not just vaccine adverse events reported to VAERS.⁶⁷ Furthermore, as explained in detail above, several factors have contributed to the number of VAERS reports submitted for the Authorized COVID-19 Vaccines. The issues raised in this article regarding underreporting of drug adverse event reporting are not directly relevant to the claims Petitioner makes regarding adverse event reporting for the Authorized COVID-19 Vaccines. The article was published in 2010 and does not consider the numerous factors outlined above regarding reporting of adverse events following COVID-19 vaccination.

Petitioner cites to a journal article in the publication *Vaccine*⁶⁸ regarding VAERS safety monitoring in support of their argument that adverse event reports for the Authorized COVID-19 Vaccines are underreported. This article generally discusses the limitations of VAERS and passive surveillance, which are well-understood by the FDA and which are discussed in this letter. Additionally, this article notes “[p]erhaps the two most common misconceptions about VAERS are that temporally associated reports represent true adverse reactions caused by vaccination, and that VAERS reports equate to rates of adverse events or indicate risk of adverse events associated with vaccination.”⁶⁹ This statement from the article demonstrates the flaws underlying Petitioner’s claims that the Authorized COVID-19 Vaccines are unsafe due to the number of serious adverse events reported to VAERS following administration of these vaccines. Additionally, the article notes “[t]he relatively rapid increase in numbers of reports to VAERS following the introduction and initial uptake of a new vaccine, an expected occurrence, has been misinterpreted as actual increases in incidence of adverse events and vaccine related risk.”⁷⁰ Thus, the article cited by Petitioner directly contradicts Petitioner’s claims regarding the safety of the Authorized COVID-19 Vaccines based on the number of VAERS adverse event reports associated with these vaccines.

⁶⁶ Lazarus et al., Electronic Support for Public Health-Vaccine Adverse Event Reporting System, Agency for Healthcare Research and Quality, HHS (Sept. 30, 2010), <https://digital.ahrq.gov/ahrq-funded-projects/electronic-support-public-health-vaccine-adverse-event-reporting-system>.

⁶⁷ Id. at 6.

⁶⁸ Shimabukuro et al., Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS), *Vaccine* (Nov. 4, 2015), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632204/>.

⁶⁹ Id. at 9.

⁷⁰ Id.

Finally, Petitioner also cites to a journal article in the American Journal of Public Health.⁷¹ This article does not raise issues that have not already been addressed in this letter's discussion of safety surveillance. For instance, the article notes that passive surveillance has several limitations, specifically, passive surveillance may involve underreporting of adverse events, and passive surveillance data is not adequate to determine causation. Additionally, this article notes that passive surveillance can provide valuable information, "[n]evertheless, if reporting is reasonably consistent, it may be possible to detect changes in trends of known common adverse events."⁷²

Therefore, the articles submitted by Petitioner do not present data or information regarding the Authorized COVID-19 Vaccines that change the Agency's analysis regarding the benefits and risks of the Authorized COVID-19 Vaccines.

Petitioner further asserts that extensive safety information regarding vaccines is inaccessible to the public ("the VAERS database is the only safety database to which the public has access. The government withholds extensive safety information from the public despite having at least ten additional data sources and expert consultants to analyze these data . . ." Petition at 2.). This contention represents a misunderstanding by Petitioner of the sources of data analyzed by FDA and its federal partners, and of the types of information available to the public.

As noted above, Petitioner's questions regarding databases operated by other federal partners, such as DOD, CMS, CDC, VA, should be directed to those federal entities. Regarding FDA's BEST system, Petitioner erroneously claims that the public does not have access to the information on this system. As noted above, the BEST system,⁷³ which is part of the Sentinel initiative,⁷⁴ comprises large-scale claims data, electronic health records (EHR), and linked claims-EHR databases with a data lag of approximately three months. The system makes use of multiple data sources and enables rapid queries to detect or evaluate adverse events as well as studies to answer specific safety questions for vaccines. The system is not intended to be a source of raw EHR data. Instead, as explained on FDA's webpage describing the BEST system, the purpose of the BEST system is to: (1) build data, analytics, infrastructure for an active, large-scale, efficient surveillance system for biologic products; and (2) develop innovative methods to utilize electronic health records (EHR) effectively and establish automated adverse events reporting, utilizing natural language processing and artificial intelligence.⁷⁵ BEST does not have access to the raw, identifiable data. BEST data partners analyze the raw data per publicly posted protocols and send the results in aggregated form to BEST for review. The information is summarized in either final reports, manuscripts or public presentations. BEST publicly posts study protocols of surveillance activities on the BEST site with open public comments regarding the protocols, final reports and manuscripts as well as communication on CBER safety site and public meetings, e.g., VRBPAC, where appropriate. These protocols delineate the scientific approach to analyzing the raw data, where in the raw form is of limited utility to the public, to

⁷¹ S. Rosenthal and R. Chen, The reporting sensitivities of two passive surveillance systems for vaccine adverse events, American Journal of Public Health (Dec. 1995), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1615747/>.

⁷² Id.

⁷³ CBER Biologics Effectiveness and Safety (BEST) System, <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system>.

⁷⁴ FDA's Sentinel Initiative, <https://www.fda.gov/safety/fdas-sentinel-initiative>.

⁷⁵ CBER Biologics Effectiveness and Safety (BEST) System, <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-biologics-effectiveness-and-safety-best-system>.

generate information on vaccine safety. The final reports and manuscripts summarize the information and conclusions inferred from well-conducted surveillance studies.

iii. FDA Has Responded to Safety Signals Related to the Authorized COVID-19 Vaccines by Extensively Reviewing Data, Updating the Authorized Labeling, and Communicating to the Public

Petitioner further asserts that “FDA and CDC have not responded to these data by issuing any warnings or restricting the use of these vaccines.” Petition at 2. This assertion is inaccurate. As explained in detail above, FDA and its federal partners, including CDC, have closely monitored post-market safety data regarding the Authorized COVID-19 Vaccines. FDA has worked to identify and investigate serious adverse events occurring in people after receiving the Authorized COVID-19 Vaccines, and to communicate these risks to the public and revise the authorized labeling to reflect these risks in a timely fashion.⁷⁶ The surveillance systems that are in place to monitor the safety of COVID-19 vaccines authorized for emergency use are working, as demonstrated by FDA’s and CDC’s work to identify and investigate these serious adverse events in a timely manner.

Adverse events reported to VAERS following administration of one of the authorized COVID-19 vaccines are reviewed to assess possible safety concerns. Such review of VAERS data regarding the authorized COVID-19 vaccines has been conducted since these vaccines were authorized. Such review has prompted the Agency to take action with respect to the currently authorized COVID-19 vaccines:

- On April 13, 2021, FDA and CDC recommended a pause in the use of the Janssen COVID-19 vaccine following six VAERS reports in the U.S. of thrombosis with thrombocytopenia.⁷⁷ The FDA and CDC thoroughly reviewed VAERS and other post-authorization information and data related to the Janssen COVID-19 vaccine during the recommended pause. This review included two meetings of ACIP. Following a thorough safety review, FDA determined that the available data show that the Janssen COVID-19 vaccine’s known and potential benefits outweigh its known and potential

⁷⁶ Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Sections 5.2 and 5.3 Warnings and Precautions Regarding Thrombosis with Thrombocytopenia and GBS, <https://www.fda.gov/media/146304/download>; Pfizer-BioNTech COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, <https://www.fda.gov/media/144413/download>; Moderna COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, <https://www.fda.gov/media/144637/download>.

⁷⁷ We note that Petitioner mentions that Denmark, among other nations, has “banned” the Janssen COVID-19 vaccine. To the extent Petitioner relies on this ban as support for Petitioner’s request that FDA revoke the EUA for this vaccine, we note that Denmark and other nations’ actions with respect to the use of this vaccine are outside purview of FDA’s work, so we cannot comment on decisions they make under their public health regulatory framework.

risks in individuals 18 years of age and older. As a result of this review, the Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) was updated to include a Warning pertaining to the risk of thrombosis with thrombocytopenia. The Fact Sheet for Recipients and Caregivers was also updated to include information about these serious adverse events. The FDA and CDC conducted extensive outreach to providers and clinicians to ensure they were made aware of the potential for these adverse events and could properly recognize and manage thrombosis with thrombocytopenia in individuals who receive the Janssen COVID-19 Vaccine.

- On June 25, 2021, following review of VAERS reports, FDA required revisions to the authorized labeling for the Pfizer-BioNTech COVID-19 vaccine and the Moderna COVID-19 vaccine to add a warning regarding the suggested increased risks of myocarditis and pericarditis. This update to the authorized labeling for these vaccines followed an extensive review of information and the discussion by CDC's ACIP meeting on June 23, 2021. As of July 26, 2021, the FDA and the Centers for Disease Control and Prevention (CDC) have received 1,194 reports of myocarditis or pericarditis occurring among people ages 30 and younger who received either Moderna or Pfizer-BioNTech COVID-19 vaccines, particularly following the second dose.⁷⁸ Through follow-up, including medical record reviews, the FDA and CDC had confirmed 699 cases of myocarditis or pericarditis.⁷⁹
- On July 13, 2021, FDA required revisions to the vaccine recipient and vaccination provider fact sheets for the Janssen COVID-19 Vaccine to include information pertaining to a suggested increased risk of Guillain-Barré Syndrome (GBS) during the 42 days following vaccination. Based on an analysis of Vaccine Adverse Event Reporting (VAERS) data, at that time, there had been 100 reports of presumptive GBS following vaccination with the Janssen vaccine after approximately 12.5 million doses administered. Of these reports, 95 of them were serious and required hospitalization. There was one reported death. As noted in the Janssen Fact Sheet for Healthcare Providers Administering Vaccine, because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Each year in the United States, an estimated 3,000 to 6,000 people develop GBS. Most people fully recover from the disorder. FDA publicly presented this issue, and information regarding these 100 reports of presumptive GBS, to the ACIP on July 22, 2021.⁸⁰

During each of these post-authorization reviews and labeling changes, the FDA has evaluated the available post-authorization information for the authorized COVID-19 Vaccines and continues to find the known and potential benefits clearly outweigh the known and potential risks.

⁷⁸ CDC, COVID-19 Reported Adverse Events, <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html>.

⁷⁹ Id.

⁸⁰ FDA, CDC ACIP Meeting Presentation, Guillain-Barré Syndrome (GBS) after Janssen COVID-19 Vaccine: Vaccine Adverse Event Reporting System (VAERS), July 22, 2021, <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/02-COVID-Alimchandani-508.pdf>.

iv. Petitioner’s Claims Regarding Anaphylaxis

Petitioner cites to a study of acute allergic reactions to mRNA COVID-19 vaccines in support of their argument that adverse event rates for COVID-19 vaccines have been miscalculated by CDC.⁸¹ As stated above, questions relating to CDC are best directed to that Agency. We note, however, that this journal article states, immediately after the sentence quoted by Petitioner, “[h]owever, the overall risk of anaphylaxis to an mRNA COVID-19 vaccine remains extremely low and largely comparable to other common health care exposures. Although cases were clinically compatible with anaphylaxis, the mechanism of these reactions is unknown.” The paper further states, in describing the limitations of the study, that “[a] northeastern US cohort may not be generalizable.” Thus, Petitioner is inappropriately generalizing the results of this study in an attempt to compare the results to the CDC’s reported data and conclude that the safety of COVID vaccines is “considerably worse than it currently appears.” Petition at 4.

Additionally, we note that the authorized labeling for all the Authorized COVID-19 vaccines already contain warnings regarding the risk of anaphylaxis as a potential adverse event. Thus, the risk of anaphylaxis is a potential safety issue FDA is already aware of, and Petitioner’s argument, and the article submitted in support of this argument, does not change FDA’s conclusions regarding the safety of the Authorized COVID-19 vaccines.

v. Animal Toxicology and Pharmacokinetic Studies of COVID-19 Vaccines

Petitioner raises concerns regarding FDA’s vaccine safety assessment. Specifically, Petitioner states that other “problems with vaccine safety assessment *may exist* because of inadequate animal toxicology and pharmacokinetic studies of COVID vaccines.” Petition at 5; emphasis added. As an initial matter, we note that Petitioner’s concerns regarding the vaccine safety assessment for COVID-19 vaccines involves speculation regarding whether problems actually exist (“problems with vaccine safety assessment *may exist* . . .”), and Petitioner fails to point to any specific problems that result or may result from the allegedly inadequate studies. Regarding Petitioner’s claims, in general, when evaluating the safety data regarding a vaccine, FDA considers data from animal studies (if such pre-clinical studies were performed) as one part of the full body of evidence regarding the vaccine. In addition to data from animal studies, if available, FDA evaluates data from in vitro studies and conducts a safety assessment of data from clinical studies.

Thus, although Petitioner raises several concerns and cites to several articles regarding risks of COVID-19 vaccination, FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. Therefore, the

⁸¹ Blumenthal KG, Robinson LB, Camargo CA, et al., Acute Allergic Reactions to mRNA COVID-19 Vaccines, JAMA. 2021;325(15):1562–1565. doi:10.1001/jama.2021.3976, <https://jamanetwork.com/journals/jama/fullarticle/2777417>.

criterion under section 564(c)(2)(B) continues to be met with respect to the Authorized COVID-19 Vaccines.

4. No Alternatives

As noted above, Petitioner requests that “FDA should revoke all EUAs and refrain from approving any future EUA . . . for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooted the EUAs.” Petition at 1. Section 564(c)(3) of the FD&C Act provides one of the required statutory factors that must be met in order for a product to be granted an EUA. This statutory provision requires that “there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating [the serious or life-threatening disease or condition].”⁸² To the extent Petitioner’s contention can be interpreted as an argument that there are adequate, approved, available drugs indicated for the prevention of COVID-19 (and that therefore the requirement in section 564(c)(3) of the FD&C Act that there is no “adequate, approved, and available alternative to the Authorized COVID-19 Vaccines for preventing COVID-19 is not met), this argument is erroneous.

As explained in the Decision Review Memoranda for the Authorized COVID-19 Vaccines, at the time each COVID-19 vaccine EUA was issued, there were no FDA-approved drugs or biological products indicated to prevent COVID-19 in any population because no vaccine or other medical product was the subject of an approved marketing application for prevention of COVID-19.⁸³ This is still true today, with the exception of the BLA for BioNTech’s COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty), which is now approved for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. The EUA for Pfizer-BioNTech COVID-19 Vaccine remains in effect. This EUA will continue to cover individuals 12 through 15 years of age, to cover the administration of a third dose to certain immunocompromised individuals 12 years of age and older, and to cover individuals 16 years of age and older until sufficient approved vaccine can be manufactured and distributed. Similarly, the EUA for the Moderna COVID-19 Vaccine and the Janssen COVID-19 Vaccine remain in effect for individuals 18 years of age and older. Although FDA has approved one new drug application (NDA) for remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization, this drug is not for prevention of COVID-19. Several other therapies are currently available under EUA, but not FDA approved, for treatment of COVID-19, and one is available under EUA, but not FDA approved, for post-exposure prophylaxis in a limited population. These products that are available under EUA are not considered “approved” products for purposes of section

⁸² The term “approved,” for purposes of section 564(c) of the FD&C Act, means a product is approved, licensed, or cleared by FDA under section 505, 510(k), or 515 of the FD&C Act or section 351 of the PHS Act, as applicable, and this term is indication-specific. *See*, section 564(a)(2) of the FD&C Act. *See also*, EUA guidance at 3.

⁸³ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 8-9, <https://www.fda.gov/media/144416/download>; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 9, <https://www.fda.gov/media/144673/download>; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 9, <https://www.fda.gov/media/146338/download>.

564(c)(3) because they are not the subject of an approved marketing application (i.e., they are not approved under an NDA or BLA).

Thus, Petitioner's assertion that the EUAs for the Authorized COVID-19 Vaccines are "mooted" by the existence of drugs approved to prevent COVID-19 is incorrect.

5. No Other Circumstances Make A Revision or Revocation Appropriate to Protect the Public Health or Safety

As noted above, section 564(g)(2)(C) of the FD&C Act provides that FDA may revise or revoke an EUA if circumstances justifying its issuance (under section 564(b)(1)) no longer exist, the criteria for its issuance are no longer met, or other circumstances make a revision or revocation appropriate to protect the public health or safety. The EUA guidance explains that such other circumstances may include:

significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.⁸⁴

As of the date of this writing, FDA has not identified any such circumstances that would make revocation of any of the Authorized COVID-19 Vaccines appropriate to protect the public health or safety. As stated previously in this response, FDA determined the EUA standard is met for the three authorized COVID-19 vaccines because data submitted by the sponsors demonstrated in a clear and compelling manner that the known and potential benefits of these products, when used to prevent COVID-19, outweigh the known and potential risks of these products, and that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating COVID-19.

As described in detail in section III.b.i.1.b above, FDA has identified circumstances that have made revision of the EUAs for the Authorized COVID-19 Vaccines appropriate, and,

⁸⁴ EUA Guidance at 29.

accordingly, has required changes to the authorized labeling for the Authorized COVID-19 Vaccines.⁸⁵

Additionally, as explained above, FDA finds no basis in the information submitted in the Petition, or in any postmarket data regarding the Authorized COVID-19 Vaccines, to support a revocation of any of these EUAs, nor has Petitioner provided any such information in the Petition. FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. Furthermore, there are no other circumstances that make a revision or revocation appropriate to protect the public health or safety, nor has Petitioner provided any information about such circumstances.

FDA therefore sees no justifiable basis upon which to take any action based on Petitioner's request with respect to the any of the Authorized COVID-19 Vaccines. Accordingly, as noted above, we deny Petitioner's request for FDA to "revoke all EUAs . . . for any COVID vaccine for all demographic groups because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs."

2. Petitioner's Request to Refrain from Granting any Future EUA for a COVID-19 Vaccine for any Population Because Approved Drugs Exist for COVID-19 Prevention

Petitioner also requests in the Petition that FDA "refrain from approving any future EUA . . . for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs."⁸⁶ Petition at 1.

Petitioner has provided no evidence that would provide a basis for FDA to conclude that no future COVID-19 vaccine candidate could meet the EUA standard. Indeed, FDA is not aware of any information indicating that the known and potential benefits of the Authorized COVID-19 Vaccines are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition.

Additionally, as explained above in section III.b.i.1.b. of this letter, to the extent Petitioner's contention can be interpreted as an argument that there are FDA-approved drugs indicated for the prevention of COVID-19 (and that therefore the requirement in section 564(c)(3) of the FD&C Act that there is no "adequate, approved, and available alternative" could not be met), this

⁸⁵ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12 -15 Years of Age (May 10, 2021), Section 4.6, EUA Prescribing Information and Fact Sheets, <https://www.fda.gov/media/148542/download>; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), <https://www.fda.gov/media/151613/download>; FDA, Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), <https://www.fda.gov/media/151611/download>.

⁸⁶ FDA authorization of an EUA request is not FDA approval. FDA does not "approve" an EUA request. Rather, FDA *authorizes* the emergency use of a product following review of data and information submitted in an EUA request.

argument fails. Should FDA receive future requests for EUAs for COVID-19 vaccine candidates, FDA would consider such requests on a case-by-case basis.⁸⁷ Accordingly, Petitioner's request is denied.

3. Petitioner's Request to Refrain from Approving any Future NDA for any COVID-19 Vaccine for any Population

Petitioner's request regarding "any future...NDA ... for any COVID Vaccine for all demographic groups" is moot because vaccines are biological products subject to licensure under the PHS Act and are not subject to approval under section 505 of the FD&C Act.

4. Petitioner's Request to Refrain from Licensing any Future BLA for any COVID-19 Vaccine for any Population

Petitioner requests that FDA "refrain from approving any future . . . BLA for any COVID vaccine for all demographic groups because the current risks of serious adverse events or deaths outweigh the benefits, and because existing, approved drugs provide highly effective prophylaxis and treatment against COVID, mooting the EUAs." Petition at 1. To the extent this request can be interpreted as asserting that the risks of serious adverse events or deaths associated with any COVID-19 vaccine would necessarily outweigh the benefits of any COVID-19 vaccine and therefore FDA should refrain from approving any BLA for any COVID-19 vaccine, this section explains why this argument is unavailing and why we are denying Petitioner's request.

To the extent this request can be interpreted as *also* asserting, in addition to the assertion above, that, because approved drugs provide effective prophylaxis and treatment of COVID-19, the approval of a BLA for a COVID-19 vaccine would be "moot," this section explains why such a position is flawed and why FDA is not granting this request.

a. Petitioner's Request that FDA Refrain from Approving any BLA for any COVID-19 Vaccine because the Current Risks Outweigh the Benefits

Petitioner requests that FDA "refrain from approving any future BLA . . . for any COVID vaccine for all demographic groups" because the risks of serious adverse events or deaths associated with any COVID-19 vaccine outweigh the benefits of any COVID-19 vaccine. Petitioner has provided no evidence that would provide a basis for FDA to conclude that no COVID-19 vaccine could meet the BLA approval standard, however. Indeed, FDA has now approved a BLA for BioNTech's COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) because, among other things, the data and information in the application demonstrated the safety and effectiveness of the vaccine.⁸⁸ Thus, Petitioner's request that FDA refrain from approving any BLAs for COVID-19 vaccines is denied.

⁸⁷ FDA has issued guidance describing factors the Agency intends to use in determining how to prioritize EUA requests for COVID-19 vaccine candidates. See October 2020 Guidance at 5 (citing EUA Guidance at 18-20).

⁸⁸ See FDA's Summary Basis for Regulatory Action (SBRA) for the BioNTech BLA. This memorandum will be posted on www.fda.gov.

In Appendix I to this letter, we have provided additional background information about FDA’s regulatory framework for the review of vaccine BLAs.

b. Petitioner’s Request that FDA Refrain from Approving any BLA for any COVID-19 Vaccine because the Current Risks Outweigh the Benefits and because Currently-Approved Drugs are Effective in Preventing COVID-19

To the extent Petitioner is arguing that FDA should *also* refrain from approving a BLA for any COVID-19 vaccine because of the existence of FDA-approved drugs that are effective in preventing COVID-19, this argument is unavailing. As described above in section III.b.i.1, there are no FDA-approved drugs that are effective in preventing COVID-19 (other than BioNTech’s COVID-19 vaccine [COVID-19 Vaccine, mRNA; Comirnaty], which is now approved for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.).

For the reasons outlined in this section, FDA denies Petitioner’s requests to refrain from licensing any BLAs for a COVID-19 vaccine.

ii. Petitioner’s Requests Regarding COVID-19 Vaccines in Children

1. Request to Immediately Refrain from Allowing COVID-19 Vaccine Trials to Include Pediatric Subjects

In the Petition, Petitioner requests that FDA “immediately refrain from allowing minors to participate in COVID vaccine trials . . .” Petition at 1. To the extent that the Petition can be interpreted to request that FDA suspend any COVID-19 vaccine clinical trial that includes pediatric subjects, this section explains why FDA is not at this time ordering that these clinical trials be suspended.

As explained above in section III.a., 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. The Petition requests that FDA adopt a universal approach toward all clinical trials of COVID-19 vaccines. Under FDA’s regulations, however, the Agency examines each Investigational New Drug (IND) Application individually and considers the IND in the context of the standards in the regulation.

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. In this section of this letter, we explain why, at this time, FDA has not granted Petitioner’s request to place all proposed or ongoing studies of COVID-19 vaccines enrolling pediatric subjects on clinical hold under 21 CFR 312.42(b).

The grounds for placing a proposed or ongoing study, including an ongoing Phase 3 study, on clinical hold are provided in 21 CFR 312.42(b). Specifically, 21 CFR 312.42(b)(1)(i) through (b)(1)(v) provides grounds for imposition of a clinical hold of a Phase 1 study. Additionally, as stated in 21 CFR 312.42(b)(2), FDA may place a proposed or ongoing Phase 2 or 3 investigation on clinical hold if it finds that: (i) any of the conditions in 21 CFR 312.42(b)(1)(i) through (b)(1)(v) apply; or (ii) the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives. As indicated in more detail below, at this time, FDA has not granted Petitioner's request to place all proposed or ongoing studies of COVID-19 vaccines enrolling pediatric subjects on clinical hold under 21 CFR 312.42(b).

- 21 CFR 312.42(b)(1)(i): Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury.

FDA continues to evaluate all available information and, based on this evaluation thus far, does not believe that human subjects in any COVID-19 vaccine study that includes pediatric subjects are or would be exposed to an unreasonable and significant risk of illness or injury. The Agency reviews the protocols for COVID-19 vaccine clinical trials proposing to enroll pediatric subjects when they are submitted to the IND, in addition to any subsequent protocol amendments. For those clinical trials that have proceeded to studying COVID-19 vaccines in pediatric populations, FDA has determined that, based on all information currently available to FDA, the studies do not expose subjects to unreasonable risks.

- 21 CFR 312.42(b)(1)(ii): The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND.

The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that clinical investigators named in the IND for any COVID-19 vaccine clinical trial including pediatric subjects are not qualified by reason of their scientific training and experience to conduct the investigation described in the INDs.

- 21 CFR 312.42(b)(1)(iii): The investigator brochure is misleading, erroneous, or materially incomplete.

The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that the investigator brochures for any ongoing COVID-19 vaccine investigation which includes or proposes to include pediatric subjects are misleading, erroneous, or materially incomplete.

- 21 CFR 312.42(b)(1)(iv): The IND does not contain sufficient information required under 312.23 to assess the risks to subjects of the proposed studies.

The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that the IND for any ongoing COVID-19 vaccine in which

pediatric subjects are enrolled contains insufficient information required under 21 CFR 312.23 to assess the risks to pediatric subjects participating in the studies.

- 21 CFR 312.42(b)(1)(v) [provides, in part, that]: The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (*i.e.*, affecting reproductive organs) or developmental toxicity (*i.e.*, affecting potential offspring)....

The Petitioner has not provided evidence and FDA is currently aware of no other information indicating that any COVID-19 vaccine studies enrolling pediatric subjects are excluding from eligibility men or women – including male and female adolescents and teenagers - with reproductive potential.

- 21 CFR 312.42(b)(2)(ii): The plan or protocol for the Phase 2 or Phase 3 investigation is clearly deficient in design to meet its stated objectives.

The Agency reviewed the protocols for the COVID-19 vaccine investigations involving pediatric subjects at the time they were submitted to the INDs, as well as any subsequent amendments as they were submitted, and has determined that the study designs meets their stated objectives.

At this time, the Agency is aware of no information to indicate that the protocols for any ongoing clinical investigations of COVID-19 vaccines involving pediatric subjects are clearly deficient in design to meet their stated objectives.

FDA has reviewed the issues raised in the Petition relating to the request to “immediately refrain from allowing minors to participate in COVID vaccine trials.” Petition at 1. For the reasons outlined above, and in light of information currently available to FDA, FDA has determined that grounds do not exist to grant Petitioner’s request to place all COVID-19 vaccine clinical investigations involving pediatric subjects on clinical hold pursuant to 21 CFR 312.42.

2. Request that FDA Refrain from Issuing EUA Amendments for Authorized COVID-19 Vaccines to Include Indications for Pediatric Populations

The Petition requests, among other things, that “[g]iven the extremely low risk of COVID illness in children, FDA should . . . immediately refrain from amending EUAs to include children. . . .” Petition at 1. To the extent that the Petition requests that FDA refrain from issuing EUA amendments for any of the Authorized COVID-19 Vaccines to include an indication for use in pediatric populations, this section explains why FDA is not granting this request.

In determining whether to issue an EUA for a product, including an amendment to an EUA in order to include additional populations within the indication, the FDA evaluates the available evidence and assesses, among other things, any known or potential risks and any known or potential benefits. Once a manufacturer submits an EUA request for a COVID-19 vaccine, the FDA then evaluates the request and determines whether the relevant statutory criteria are met,

taking into account the totality of the scientific evidence about the vaccine that is available to the agency.

As noted in Section II.b. above, in the October 2020 Guidance, FDA provided recommendations that describe key information that would support issuance of an EUA for a vaccine to prevent COVID-19.⁸⁹ In this guidance, FDA explained that, in the case of such 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.⁹⁰ 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.⁹¹

a. Information Submitted by Petitioner Regarding the Safety of COVID-19 Vaccines in Pediatric Populations

Petitioner argues that, for children, the risks of COVID-19 vaccines outweigh the benefits because the risk of severe COVID in children is “extremely low.” Petition at 1. Petitioner cites to several sources of information in support of this argument (Petition at 12-13), which FDA has reviewed and considered.

Petitioner cites to CDC data⁹² regarding death rates of children in the United States due to COVID-19 and compares the number of children who have died involving COVID-19 to the number of Americans of all ages who have died of COVID-19. Petitioner's approach of simply comparing raw numbers of deaths involving COVID-19 in the U.S. pediatric population against the raw numbers of deaths involving COVID-19 in the overall U.S. population (all sexes and all ages), does not provide a sufficient scientific basis upon which to conclude, as Petitioner contends, that the “relative risk for children due to COVID is very low.” Petition at 12. Additionally, as discussed in further detail below, based on available data and information, we have concluded that COVID-19 is a serious or life-threatening disease or condition in the 12-17 age group.

As a preliminary matter, we note that petitioner's claim that “the death rate following either vaccination in this age group, assuming these children were trial enrollees, is approximately 2 in 2,000 or 0.1%.” (Petition at 13) is erroneous. Our review of the submitted clinical trial data associated with the Pfizer-BioNTech COVID-19 Vaccine has not identified any deaths among adolescent or young adult vaccinees.⁹³ Additionally, as described in a NEJM article regarding

⁸⁹ October 2020 Guidance at 6-7.

⁹⁰ Id. at 3.

⁹¹ Id. at 4.

⁹² CDC, National Center for Health Statistics, Weekly Updates by Select Demographic and Geographic Characteristics, https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#SexAndAge.

⁹³ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), <https://www.fda.gov/media/144416/download> (stating that there were two deaths in vaccine recipients, both >55 years of age). FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for

the Moderna COVID-19 vaccine, no deaths were reported among vaccine recipients enrolled in the clinical trial of Moderna COVID-19 Vaccine.⁹⁴ Investigational New Drug (IND) application sponsors are required to notify FDA in a written safety report of any adverse experience associated with the use of the drug that is both serious and unexpected.⁹⁵ Any death that occurs in a vaccine clinical trial therefore must be reported to FDA and is then thoroughly evaluated by FDA to determine the cause and whether or not the death is plausibly related to the vaccine.

Additionally, we note that Petitioner raised concerns regarding VAERS reports in arguing that COVID-19 vaccines should not be authorized for pediatric populations because, Petitioner argues, “[a]vailable evidence strongly suggests that the vaccine is much more dangerous to children than the disease.” Petition at 12. VAERS data reviewed to date has not identified risks related to vaccination that would cause the Agency to change its view that the benefits of vaccination with the Pfizer-BioNTech COVID-19 vaccine outweigh the risks of vaccination in individuals 12-17 years of age. VAERS data is evaluated thoroughly, and as described in greater detail above, FDA acts on safety signals. VAERS reports, however, are not used *in isolation* to draw an association between a vaccine and a possible adverse event.

Finally, we note that petitioner cites to an opinion piece published in the British Medical Journal, which presents the authors’ opinion that the benefits of COVID-19 vaccination are outweighed by its risks in pediatric populations.⁹⁶ FDA has reviewed this article and determined it does not present evidence that the EUA standard could not be met for pediatric populations. Indeed, as explained in the FDA Decision Memorandum for the Pfizer-BioNTech COVID-19 Vaccine EUA, based on FDA’s review of all available data regarding the benefits and risks of the use of the Pfizer-BioNTech COVID-19 vaccine in individuals 12 through 17 years of age, we have determined that this EUA meets the statutory criteria for individuals in this age range.⁹⁷

Petitioner has failed to present data demonstrating that, for children, the risks of COVID-19 vaccines outweigh their benefits because the risk of severe COVID in children is “extremely low.” Petition at 1. As explained in this section, the information submitted by Petitioner does not support this contention. As explained in further detail below, data reviewed by the Agency demonstrates that the Pfizer-BioNTech COVID-19 Vaccine, which is authorized for use in individuals 12 years of age and older, continues to demonstrate that the known and potential benefits of this vaccine outweigh its known and potential risks in this population. Any other EUA requests for COVID-19 vaccine candidates for use in pediatric populations will be reviewed on a case-by-case basis under the applicable statutory standards. Therefore, we deny

Authorization in Individuals 12-15 Years of Age (May 10, 2021), <https://www.fda.gov/media/148542/download> (stating that there were no deaths among vaccine recipients 12-15 years of age during the follow-up period).

⁹⁴ K. Ali, et al., Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents, *NEJM* (Aug. 11, 2021), DOI: 10.1056/NEJMoa2109522, <https://www.nejm.org/doi/10.1056/NEJMoa2109522>.

⁹⁵ 21 CFR § 312.32(c)(1)(i).

⁹⁶ W. Pegden, V. Prasad, S. Baral, Covid vaccines for children should not get emergency use authorization, *BMJ* (May 7, 2021), <https://blogs.bmj.com/bmj/2021/05/07/covid-vaccines-for-children-should-not-get-emergency-use-authorization/>.

⁹⁷ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), <https://www.fda.gov/media/144416/download>; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), <https://www.fda.gov/media/148542/download>.

Petitioner’s request to refrain from amending any EUA for a COVID-19 vaccine to include a pediatric indication.

3. Request that FDA Immediately Revoke all EUAs for COVID-19 Vaccines with Pediatric Indications

Petitioner requests that FDA “immediately revoke all EUAs that permit vaccination of children under 16 for the Pfizer vaccine and under 18 for other COVID vaccines.” Petition at 1. Currently, only the Pfizer-BioNTech COVID-19 vaccine is indicated for the prevention of COVID-19 in pediatric populations. This vaccine is indicated for individuals 12 years of age and older. As explained in section III.B.i.1.b above, in addressing this request, it is necessary to consider the EUA revocation standard provided in section 564(g)(2) of the FD&C Act. In this section, we assess whether any of these statutory conditions under which FDA may revoke an EUA are met with respect to the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA and explain why the EUA revocation standard is not met for this vaccine.

a. Standard for Revocation of EUAs is not Met for the Authorized COVID-19 Vaccines with Pediatric Indications

As explained above in section III.b.i.1.b of this letter, Section 564(g)(2) of the FD&C Act provides the standard for revocation of an EUA. Under this statutory authority, FDA may revise or revoke an EUA if:

- (A) the circumstances described under [section 564(b)(1) of the FD&C Act] no longer exist;
- (B) the criteria under [section 564(c) of the FD&C Act] for issuance of such authorization are no longer met; or
- (C) other circumstances make such revision or revocation appropriate to protect the public health or safety.

As explained above in section II.b., the EUA Guidance notes that once an EUA is issued for a product, in general, that EUA will remain in effect for the duration of the EUA declaration under which it was issued, “unless the EUA is revoked because the criteria for issuance . . . are no longer met or revocation is appropriate to protect public health or safety (section 564(f),(g) [of the FD&C Act]).”⁹⁸

i. Circumstances Continue to Justify the Issuance of the EUAs for the Authorized COVID-19 Vaccine with Pediatric Indications

As explained in detail above in section III.b.i.1.b., section 564(b)(2) of the FD&C Act sets forth the statutory standard for termination of an EUA declaration. This provision provides that an EUA declaration remains in place until the earlier of: (1) a determination by the HHS Secretary, in consultation with the Secretary of Defense, that the circumstances that precipitated the declaration have ceased or (2) a change in the approval status of the product such that the authorized use(s) of the product are no longer unapproved. Neither of those statutory criteria is

⁹⁸ EUA Guidance at 28.

satisfied with respect to the Authorized COVID-19 Vaccine with a pediatric indication. Thus, the circumstances described under section 564(b)(1) of the FD&C Act continue to exist. FDA therefore is not revoking the EUA for the Authorized COVID-19 vaccine with a pediatric indication under the authority in section 564(g)(2)(A) of the FD&C Act.

1. The Criteria for The Issuance of the Authorized COVID-19 Vaccine with Pediatric Indications Continues to Be Met

This section describes in detail why the criteria under section 564(c) of the FD&C Act continue to be met with respect to the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA and why, therefore, FDA may not revoke this EUA under the authority in section 564(g)(2)(B) of the FD&C Act.

a. Serious or life-threatening disease or condition.

As explained above in section III.b.i.1 of this letter, section 564(c)(1) of the FD&C Act requires that, for an EUA to be issued for a medical product, “the agent(s) referred to in [the HHS Secretary’s EUA declaration] can cause a serious or life-threatening disease or condition.” FDA has concluded that SARS-CoV-2, which is the subject of the EUA declaration, meets this standard. FDA is not aware of science indicating that there is any change in the ability of the SARS-CoV-2 virus to cause a serious or life-threatening disease or condition, namely COVID-19, nor has Petitioner provided any information about such a change.

The SARS-CoV-2 pandemic continues to present an extraordinary challenge to global health and, as of August 3, 2021, has caused more than 199 million cases of COVID-19 and claimed the lives of more than 4.2 million people worldwide.⁹⁹ In the United States, more than 34 million cases and over 611,000 deaths have been reported to the CDC.¹⁰⁰ On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS, and the U.S. President declared a national emergency in response to COVID-19 on March 13, 2020. Additional background information on the SARS-CoV-2 virus and COVID-19 pandemic may be found in FDA Decision Memoranda for the Authorized COVID-19 Vaccines.¹⁰¹

Since March 1, 2020, approximately 1.7 million COVID-19 cases in individuals 12 to 17 years of age have been reported to the Centers for Disease Control and Prevention (CDC). Among these cases approximately 11,700 resulted in hospitalization, with more than 691 ICU admissions

⁹⁹ Johns Hopkins University School of Medicine, Coronavirus Resource Center, <https://coronavirus.jhu.edu/map.html>.

¹⁰⁰ CDC, COVID Data Tracker, https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases.

¹⁰¹ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), <https://www.fda.gov/media/144416/download>; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), <https://www.fda.gov/media/148542/download>; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), <https://www.fda.gov/media/144673/download>; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), <https://www.fda.gov/media/146338/download>.

and more than 100 deaths. It is difficult to estimate the incidence of COVID-19 among children and adolescents because they are frequently asymptomatic and infrequently tested. Children and adolescents appear less susceptible to SARS-CoV-2 infection and have a milder COVID-19 disease course as compared with adults. However, as with adults, children and adolescents with underlying conditions such as asthma, chronic lung disease, and cancer are at higher risk than their healthier counterparts for COVID-19-related hospitalization and death. Of the children who have developed severe illness from COVID-19, most have had underlying medical conditions. Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious COVID-19-associated condition that can present with persistent fever, laboratory markers of inflammation and heart damage, and, in severe cases, hypotension and shock. As of June 28, 2021, the CDC received reports of 4196 cases and 37 deaths that met the definition for MIS-C.

Both FDA and CDC have convened advisory committee meetings to discuss the use of COVID-19 vaccines in pediatric populations. Overall, these advisory committees agreed that there is a serious risk of severe COVID-19 in the pediatric population. In particular, the June 23, 2021 ACIP meeting discussed the benefits and risks of the use of COVID-19 mRNA vaccines in adolescents and young adults.¹⁰² This discussion raised the point that adolescents and young adults have the highest COVID-19 incidence rates, and that these populations are an increasing proportion of COVID-19 cases reported. COVID-19-associated deaths continue to occur in these populations; since April 2021, 316 deaths have been reported among persons aged 12-29 years. Additionally, post-COVID conditions -- such as Multisystem Inflammatory Syndrome in Children (MIS-C) and Multisystem Inflammatory Syndrome in Adults (MIS-A) -- can occur in these populations following COVID-19.

Therefore, the criterion under section 564(c)(1) continues to be met with respect to the Authorized COVID-19 Vaccines with Pediatric Indications.

b. Evidence of Effectiveness

As explained above in section III.b.i.1.b of this letter, Section 564(c)(2)(A) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude “based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.” FDA has determined that based on the totality of scientific evidence available, including data from adequate and well-controlled trials, it is reasonable to believe that the Pfizer-BioNTech COVID-19 vaccine may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition in the 12 through 17 years of age population.¹⁰³ The basis for this determination is explained in detail in FDA’s decision memoranda regarding

¹⁰² CDC, Megan Wallace and Sara Oliver, CDC ACIP Meeting Presentation, COVID-19 mRNA Vaccines in Adolescents and Young Adults: Benefit-Risk Discussion, (June 23, 2021), <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/05-COVID-Wallace-508.pdf>; CDC, ACIP Meeting Slides, (June 23, 2021), <https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html>.

¹⁰³ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), <https://www.fda.gov/media/144416/download>; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), <https://www.fda.gov/media/148542/download>.

the Pfizer BioNTech COVID-19 Vaccine EUA.¹⁰⁴ Section III.b.ii of this letter explains why Petitioner’s arguments regarding the effectiveness of the Authorized COVID-19 Vaccines, and the information submitted by Petitioner in support of this argument, does not change FDA’s analysis regarding the effectiveness of the Pfizer-BioNTech COVID-19 vaccine in individuals 12 through 17 years of age.

Therefore, the criterion under section 564(c)(2)(A) continues to be met with respect to the Authorized COVID-19 Vaccines.

c. Benefit-Risk Analysis

Section 564(c)(2)(B) of the FD&C Act requires that, for an EUA to be issued for a medical product, FDA must conclude “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” Petitioner argues that the current risks of serious adverse events or deaths associated with the authorized COVID-19 vaccines outweigh the benefits of COVID-19 vaccines in the pediatric population. Section III.b.i.1.b.ii above addresses these arguments insofar as they apply to the Authorized COVID-19 Vaccines generally and explains why they are unavailing. Section III.b.ii above addresses Petitioner’s arguments regarding the safety of COVID-19 vaccines in the pediatric population, and explains why the information submitted by Petitioner does not change FDA’s analysis regarding the benefits and risks of the authorized COVID-19 vaccines in the pediatric population.

d. No Alternatives

Section 564(c)(3) of the FD&C Act provides one of the required statutory factors that must be met in order for a product to be granted an EUA. This statutory provision requires that “there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating [the serious or life-threatening disease or condition].” To the extent Petitioner’s contention can be interpreted as an argument that there are FDA-approved drugs indicated for the prevention of COVID-19 in pediatric populations (and that therefore the requirement in section 564(c)(3) of the FD&C Act is not met with respect to the Authorized COVID-19 Vaccine with a pediatric indication), this argument is erroneous.

As described above in section III.b.i.1.b, there are no FDA-approved drugs or biological products indicated to prevent COVID-19 in any population, other than the newly-approved BioNTech COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty). That vaccine is approved for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older.¹⁰⁵ The EUA for Pfizer-BioNTech COVID-19 Vaccine remains in effect to cover those 12 through

¹⁰⁴ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), <https://www.fda.gov/media/144416/download>; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), <https://www.fda.gov/media/148542/download>.

¹⁰⁵ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), at 8-9, <https://www.fda.gov/media/144416/download>; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), at 9, <https://www.fda.gov/media/144673/download>; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), at 9, <https://www.fda.gov/media/146338/download>.

15 years of age, the administration of a third dose to certain immunocompromised individuals 12 years of age and older, and until sufficient approved vaccine can be manufactured and distributed for use in those 16 years of age and older. Similarly, the EUA for the Moderna COVID-19 Vaccine and the Janssen COVID-19 Vaccine remain in effect for individuals 18 years of age and older. Therefore, there is no adequate, approved, and available alternative to the Authorized COVID-19 Vaccines for preventing COVID-19.

ii. No Other Circumstances Make A Revision or Revocation Appropriate to Protect the Public Health or Safety

As noted above in section III.b.i.1.b of this letter, section 564(g)(2)(C) of the FD&C Act provides that FDA may revise or revoke an EUA if circumstances justifying its issuance (under section 564(b)(1)) no longer exist, the criteria for its issuance are no longer met, or other circumstances make a revision or revocation appropriate to protect the public health or safety. The EUA guidance explains that such other circumstances may include:

significant adverse inspectional findings (e.g., when an inspection of the manufacturing site and processes has raised significant questions regarding the purity, potency, or safety of the EUA product that materially affect the risk/benefit assessment upon which the EUA was based); reports of adverse events (number or severity) linked to, or suspected of being caused by, the EUA product; product failure; product ineffectiveness (such as newly emerging data that may contribute to revision of the FDA's initial conclusion that the product "may be effective" against a particular CBRN agent); a request from the sponsor to revoke the EUA; a material change in the risk/benefit assessment based on evolving understanding of the disease or condition and/or availability of authorized MCMs; or as provided in section 564(b)(2), a change in the approval status of the product may make an EUA unnecessary.¹⁰⁶

As of the date of this writing, FDA has not identified any such circumstances that would make revocation of the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA appropriate to protect the public health or safety. As stated previously in this response, FDA determined the EUA standard is met for the Pfizer-BioNTech COVID-19 Vaccine in individuals 12 through 17 years of age because data submitted by the sponsors demonstrated in a clear and compelling manner that the known and potential benefits of this vaccine, when used to prevent COVID-19, outweigh the known and potential risks of this vaccine in individuals 12 through 17 years of age, and that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating COVID-19 in this population.

As described in detail in section III.b.i.1 above, FDA has identified circumstances that have made revision of the EUAs for the Authorized COVID-19 Vaccines appropriate, and,

¹⁰⁶ EUA Guidance at 29.

accordingly, has required changes to the authorized labeling for the Authorized COVID-19 Vaccines.¹⁰⁷

Additionally, as explained above, FDA finds no basis in the information submitted in the Petition, or in any postmarket data regarding the Pfizer-BioNTech COVID-19 Vaccine, to support a revocation of the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA, nor has Petitioner provided any such information in the Petition. FDA is not aware of any information indicating that the known and potential benefits of Pfizer-BioNTech COVID-19 Vaccine in the 12-17 years of age population are outweighed by their known and potential risks, nor has Petitioner provided any such information in the Petition. Furthermore, there are no other circumstances that make a revision or revocation of the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA appropriate to protect the public health or safety, nor has Petitioner provided any information about such circumstances. FDA therefore sees no justifiable basis upon which to take any action based on Petitioner's request with respect to the pediatric indication for the Pfizer-BioNTech COVID-19 Vaccine EUA. Accordingly, as noted above, we deny Petitioner's request that FDA "immediately revoke all EUAs that permit vaccination of children under 16 for the Pfizer vaccine and under 18 for other COVID vaccines." Petition at 1.

iii. Petitioner's Request that FDA Immediately Revoke Tacit Approval that Pregnant Women may Receive any EUA or Licensed COVID-19 Vaccines and Immediately Issue Public Guidance

Petitioner requests that FDA "immediately revoke tacit approval that pregnant women may receive any EUA or licensed COVID vaccines and immediately issue public guidance to that effect." Petition at 1. Because "tacit approval," or revocation thereof, is not a concept that exists in applicable statutes or regulations governing FDA-regulated products, FDA interprets this as a request that the labeling for the Authorized COVID-19 Vaccines, and any COVID-19 vaccine that may be licensed in the future, contain a contraindication for use during pregnancy.

In addressing Petitioner's request for a contraindication, we first discuss the risks posed to pregnant women by COVID-19. We then provide an explanation of the regulatory framework for prescription drug labeling for approved and licensed products, including the standard for inclusion of contraindications in such labeling to inform health care providers of information such as known hazards in the use of a particular drug as well as the requirements for pregnancy and lactation information in such labeling. We then discuss labeling for products made available under an EUA and explain why a contraindication for use in pregnant women was not included in the labeling for the Authorized COVID-19 Vaccines. This section concludes with an explanation for why Petitioner's requests for a contraindication for use during pregnancy in the labeling for the Authorized COVID-19 Vaccines – and BioNTech's COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) - is denied.

¹⁰⁷ FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization in Individuals 12-15 Years of Age (May 10, 2021), <https://www.fda.gov/media/148542/download>; FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), <https://www.fda.gov/media/151613/download>; FDA, Moderna COVID-19 Vaccine EUA Amendment Decision Memorandum for Authorization of an Additional Dose in Certain Immunocompromised Individuals (August 12, 2021), <https://www.fda.gov/media/151611/download>; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), <https://www.fda.gov/media/146338/download>.

Reactions; and Use in Specific Populations, which includes a subsection on Pregnancy (see § 201.57(c)(1), (5), (6), (7), and (9)(i)).

a. Contraindications

The Contraindications section must describe any situations in which the drug should not be used because the risk of use “clearly outweighs any possible therapeutic benefit” (§ 201.57(c)(5)). This section should include observed and anticipated risks, but not theoretical risks.¹¹² This could include, for example, a situation where animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans (e.g., animal data demonstrate that the drug has teratogenic effects) and those risks do not outweigh any potential benefit of the drug to any patient.¹¹³

b. Pregnancy

The Pregnancy subsection is located under the Use in Specific Populations section (see § 201.57(c)(9)(i)). On December 4, 2014, FDA issued a final rule amending the regulations on the requirements for pregnancy and lactation information in prescription drug and biological product labeling (Pregnancy and Lactation Labeling Rule (PLLR)).¹¹⁴ The PLLR revisions to the regulations were intended “to create a consistent format for providing information about the effects of a drug on pregnancy and lactation that would be useful for decision making by health care providers and their patients.”¹¹⁵ The labeling content and format requirements in § 201.57(c)(9)(i), as revised by the PLLR, took effect on June 30, 2015, with a phased implementation schedule for drugs (including biological products) that are the subject of NDAs, BLAs, and efficacy supplements that had been approved on or after June 30, 2001.¹¹⁶ The PLLR also requires for all human prescription drug and biological products, including those for which an application was approved before June 30, 2001, that the Pregnancy subsection of labeling be revised to remove the pregnancy letter categories A, B, C, D, and X.¹¹⁷ Information in the Pregnancy subsection of labeling may present, in greater detail, a topic that is briefly summarized in another section of labeling (e.g., Warnings and Precautions).¹¹⁸ FDA has explained that when a topic is discussed in more than one section of labeling, the section containing the most important information relevant to prescribing should typically include a succinct description and should cross-reference sections that contain additional detail.¹¹⁹

¹¹² See § 201.57(c)(5); see also FDA guidance for industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - Content and Format; Guidance for Industry, October 2011 (Warnings Guidance), at 8, <https://www.fda.gov/media/71866/download>.

¹¹³ See Warnings Guidance at 8.

¹¹⁴ Final rule, “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling” (PLLR) (79 FR 72064, December 4, 2014), <https://www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for>.

¹¹⁵ Id. at 72066.

¹¹⁶ See §§ 201.56(b) and 201.57(c)(9)(i).

¹¹⁷ §§ 201.57(c)(9) and 201.80; see also 79 FR 72064 at 72095 (December 4, 2014).

¹¹⁸ PLLR, 79 FR 72064 at 72085 (December 4, 2014).

¹¹⁹ See FDA guidance for industry, Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements; Guidance for Industry, February 2013, <https://www.fda.gov/media/71836/download>.

Under current labeling requirements, information in the Pregnancy subsection of labeling is presented under the following subheadings: Pregnancy Exposure Registry; Risk Summary; Clinical Considerations; and Data.¹²⁰ The labeling for the Authorized COVID-19 Vaccines includes the Pregnancy Exposure Registry and the Risk Summary subheadings. We briefly describe these subheadings below.

i. Pregnancy Exposure Registry

If there is a scientifically acceptable pregnancy exposure registry for the drug, the labeling must state that fact and provide contact information needed for enrolling in or obtaining information about the registry.

ii. Risk Summary

The Risk Summary subheading is required under the Pregnancy subsection because certain statements must be included even when no product-specific data are available, given that all pregnancies have a background risk of birth defect, loss, or other adverse outcomes.¹²¹ The Risk Summary must contain risk statement(s) that describe for the drug the risk of adverse developmental outcomes based on all relevant human data, animal data, and/or the drug's pharmacology.¹²² When multiple data sources are available, the risk statements are required to be presented in the following order: human, animal, and pharmacologic.¹²³

When human data are available that establish the presence or absence of any adverse developmental outcome(s) associated with maternal use of the drug, a risk statement based on human data must summarize the specific developmental outcome(s) and include its incidence and the effects of dose, duration of exposure, and gestational timing of exposure.¹²⁴ If human data indicate that there is an increased risk for a specific adverse developmental outcome in infants born to women exposed to the drug during pregnancy, the risk summary must contain a quantitative comparison of that risk to the risk for the same outcome in infants born to women who were not exposed to the drug, but who have the disease or condition for which the drug is indicated to be used.¹²⁵ When risk information is not available for women with the disease or condition(s) for which the drug is indicated, the risk summary must contain a comparison of the specific outcome in women exposed to the drug during pregnancy against the rate at which the outcome occurs in the general population.¹²⁶

When animal data are available, the risk statement based on such data must describe the potential risk for adverse developmental outcomes in humans and summarize the available data.¹²⁷ This statement must include: the number and type(s) of species affected; timing of exposure; animal doses expressed in terms of human dose or exposure equivalents; and outcomes for pregnant animals and offspring.¹²⁸

¹²⁰ § 201.57(c)(9)(i).

¹²¹ § 201.57(c)(9)(i)(B).

¹²² Id.

¹²³ Id.

¹²⁴ § 201.57(c)(9)(i)(B)(1).

¹²⁵ Id.

¹²⁶ Id.

¹²⁷ § 201.57(c)(9)(i)(B)(2).

¹²⁸ Id.

With respect to pharmacology, when the drug has a well-understood pharmacologic mechanism of action that may result in adverse developmental outcomes, the Risk Summary must explain the mechanism of action and the potential associated risks.¹²⁹

3. Inclusion of Contraindications and Pregnancy Information in the Labeling for the Authorized COVID-19 Vaccines

For the emergency use of an unapproved product, section 564(e)(1)(A)(i) of the FD&C Act requires that FDA must—to the extent practicable given the applicable circumstances of the emergency, and as FDA finds necessary and appropriate to protect the public health—establish appropriate conditions designed to ensure that health care professionals administering the authorized product are informed:

- That FDA has authorized the emergency use of the product (including the product name and an explanation of its intended use);
- Of the significant known and potential benefits and risks of the emergency use of the product, and the extent to which such benefits and risks are unknown; and
- Of available alternatives and their benefits and risks.

Therefore, as explained in the EUA Guidance, FDA recommends that “a request for an EUA include a ‘Fact Sheet’ for health care professionals or authorized dispensers that includes essential information about the product. In addition to the required information, Fact Sheets should include . . . any contraindications or warnings.”¹³⁰ The EUA guidance also recommends that, for unapproved drugs that do not have “FDA-approved labeling for any indication . . . in addition to the brief summary information found in a Fact Sheet, the sponsor also develop more detailed information similar to what health care professionals are accustomed to finding in FDA-approved package inserts.”¹³¹

The sponsors for all the Authorized COVID-19 Vaccines submitted such prescribing information in the EUA requests, and FDA reviewed and authorized this labeling. The Fact Sheets for Healthcare Providers Administering Vaccine for all of the Authorized COVID-19 Vaccines contain Contraindications and Warnings and Precautions sections because FDA determined that sufficient data existed for inclusion of such information in the authorized labeling for these vaccines.¹³²

FDA did not, however, require inclusion of a contraindication for pregnancy in the authorized labeling. The authorized COVID-19 vaccines are authorized for use in an age range that includes women of childbearing age and are not contraindicated for use in pregnant women because FDA

¹²⁹ § 201.57(c)(9)(i)(B)(3).

¹³⁰ EUA Guidance at 22.

¹³¹ EUA Guidance at 23.

¹³² Janssen COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Sections 5.2 and 5.3 Warnings and Precautions Regarding Thrombosis with Thrombocytopenia and GBS, <https://www.fda.gov/media/146304/download>; Pfizer-BioNTech COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, <https://www.fda.gov/media/144413/download>; Moderna COVID-19 Vaccine Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers), Section 5.2, Warning and Precautions Regarding Myocarditis and Pericarditis, <https://www.fda.gov/media/144637/download>.

is not aware of any evidence that suggests the risk of use of the Authorized COVID-19 Vaccines in pregnant women would clearly outweigh any possible therapeutic benefit.¹³³ Nor has the Petitioner presented any such evidence in the Petition. Accordingly, this request is denied.

4. Inclusion of Contraindications and Pregnancy Information in the Labeling for Licensed COVID-19 Vaccines

With respect to Petitioner’s request that FDA “immediately revoke tacit approval that pregnant women may receive any EUA or licensed COVID vaccines and immediately issue public guidance to that effect” (Petition at 1; emphasis added), as explained above in this section, FDA regulations require the Contraindications section of the labeling for an approved drug or biological product to describe any situations in which the drug or biological product should not be used because the risk of use “clearly outweighs any possible therapeutic benefit” (§ 201.57(c)(5)). This section should include observed and anticipated risks, but not theoretical risks.¹³⁴ The approved COVID-19 vaccine (COVID-19 Vaccine, mRNA; Comirnaty) is indicated for use in an age range that includes women of childbearing age and is not contraindicated for use in pregnant women because FDA is not aware of any evidence that suggests the risk of use of BioNTech’s COVID-19 vaccine in pregnant women would clearly outweigh any possible therapeutic benefit,¹³⁵ nor has the Petitioner presented any such evidence in the Petition.

In its review of a BLA for any future COVID-19 vaccine candidate, FDA will apply the regulatory standards outlined above in determining, on a case-by-case basis, whether to include a contraindication in pregnancy, or any other contraindications, in the approved labeling for such a vaccine. Accordingly, Petitioner’s request is denied.

iv. Petitioner’s Request that FDA Immediately Amend its Guidance regarding Certain Approved Drugs [chloroquine drugs, ivermectin, “and any other drugs demonstrated to be safe and effective against COVID”]

Petitioner requests that the Agency “immediately amend its existing guidance for the use of the chloroquine drugs, ivermectin, and any other drugs demonstrated to be safe and effective against COVID, to comport with current scientific evidence of safety and efficacy at currently used doses and immediately issue notifications to all stakeholders of this change.” Petition at 2. FDA has not issued “guidance for the use of chloroquine drugs, ivermectin, and other drugs

¹³³ FDA’s decision memoranda for the Authorized COVID-19 Vaccines discuss FDA’s analysis of all available data regarding the use of the Authorized COVID-19 Vaccines in pregnancy. See, FDA, Pfizer-BioNTech COVID-19 Vaccine EUA Decision Memorandum (Dec. 11, 2020), <https://www.fda.gov/media/144416/download>; FDA, Moderna COVID-19 Vaccine EUA Decision Memorandum (Dec. 18, 2020), <https://www.fda.gov/media/144673/download>; FDA, Janssen COVID-19 Vaccine EUA Decision Memorandum (Feb. 27, 2021), <https://www.fda.gov/media/146338/download>.

¹³⁴ See § 201.57(c)(5); see also Warnings Guidance at 8.

¹³⁵ See FDA’s Summary Basis for Regulatory Action (SBRA) for the BioNTech BLA. This memorandum will be posted on www.fda.gov.

demonstrated to be safe and effective against COVID.”¹³⁶ FDA has, however, analyzed adverse event information and made publicly available safety issues regarding the use of hydroxychloroquine and chloroquine to treat patients with COVID-19.¹³⁷ FDA has also informed the public that it has received multiple reports of patients who have required medical support and been hospitalized after self-medicating with ivermectin intended for horses, that taking large doses of ivermectin can cause serious harm, that ivermectin is not authorized or approved by FDA to treat COVID-19, and that using any treatment for COVID-19 that is not approved or authorized by the FDA, unless part of a clinical trial, can cause serious harm.¹³⁸ You have not provided any evidence to suggest that the safety information in these communications is inaccurate. Thus, to the extent you are requesting that FDA withdraw or revise these previous safety communications, that request is denied.

v. Petitioner’s Request that FDA Issue Guidance to the Secretary of Defense and the President

Petitioner requests that FDA “issue guidance to the Secretary of the Defense and the President not to grant an unprecedented Presidential waiver of prior consent regarding COVID vaccines for Servicemembers under 10 U.S.C. § 1107(f) or 10 U.S.C. § 1107a.” Petition at 2.

FDA denies this request because FDA, an agency within the U.S. Department of Health and Human Services, does not issue guidance of the type requested to the President of the United States or to other Departments in the executive branch of the U.S. federal government.

¹³⁶ Under FDA’s good guidance practices regulations, a “guidance document” is defined as “documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency’s interpretation of or policy on a regulatory issue.” 21 CFR 10.115(a)(b)(1). The regulation provides further that “[g]uidance documents include, but are not limited to, documents that relate to: The design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement policies.” Importantly, the provision at 21 CFR 10.115(b)(3), excludes from the definition of “guidance document” general information documents provided to consumers or health professionals, such as those communications that have been provided to the public regarding the use of hydroxychloroquine, chloroquine, and ivermectin to treat patients with COVID-19. 21 CFR 10.115(b)(3) states: “[g]uidance documents do not include: Documents relating to internal FDA procedures, agency reports, general information documents provided to consumers or health professionals, speeches, journal articles and editorials, media interviews, press materials, warning letters, memoranda of understanding, or other communications directed to individual persons or firms.” (Emphasis added.)

¹³⁷ FDA Drug Safety Communication, FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems, April 24, 2020, updated June 15, 2020 and July 1, 2020, <https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or>; FDA, CDER Office of Surveillance and Epidemiology Pharmacovigilance Memorandum, May 19, 2020, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/OSE%20Review_Hydroxychloroquine-Chloroquine%20-%2019May2020_Redacted.pdf.

¹³⁸ FDA Consumer Update, Why You Should Not Use Ivermectin to Treat or Prevent COVID-19, March 5, 2021, <https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19>; FDA Letter to Stakeholders, Do Not Use Ivermectin Intended for Animals as Treatment for COVID-19 in Humans, April 10, 2020, <https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-covid-19-humans>.

vi. Petitioner’s Request that FDA Issue Guidance to Stakeholders Regarding the Option to Refuse or Accept Administration of Investigational COVID-19 Vaccines

Petitioner requests that FDA “issue guidance to all stakeholders in digital and written formats to affirm that all citizens have the option to accept or refuse administration of investigational COVID vaccines without adverse work, educational or other non-health related consequences, under 21 U.S.C. § 360bbb-3(e)(1)(a)(ii)(III) 1 and the informed consent requirements of the Nuremberg Code.”¹³⁹ We interpret this request to relate to the Authorized COVID-19 Vaccines and third parties’ decisions with respect to unvaccinated individuals’ participation in certain activities. Such decisions by third parties with respect to employment, education, and other non-FDA-regulated activities would not be within FDA’s purview. Accordingly, FDA denies Petitioner’s request.

vii. Petitioner’s Request that FDA Issue Guidance Regarding Marketing and Promotion of COVID-19 Vaccines

FDA notes that your Petition discusses statements made by CDC. For requests intended for CDC, you should contact CDC directly.

As explained above in section III.b.i.1.b of this response, the EUA revocation standard in section 564(g)(2) of the FD&C Act is not met for any of the Authorized COVID-19 Vaccines. With respect to Petitioner’s request to issue guidance pending revocation of the EUAs for the Authorized COVID-19 Vaccines, we note that the EUA Guidance contains a section regarding advertising for EUA products. As explained in the EUA guidance, FDA may, under section 564(e)(1)(B) of the FD&C Act, on a case-by-case basis and to the extent feasible given the circumstances of a particular public health emergency, establish certain additional conditions that FDA finds to be necessary or appropriate to protect the public health.¹⁴⁰ The EUA guidance explains that, under section 564(e)(4) of the FD&C Act, FDA may place conditions on “advertisements and other promotional descriptive printed matter (e.g., press releases issued by the EUA sponsor) relating to the use of an EUA product, such as requirements applicable to prescription drugs under section 502(n)”¹⁴¹ FDA’s authority under section 564(e)(4) ordinarily does not extend to statements by third parties who have no direct connection with the EUA sponsor.

For the Authorized COVID-19 Vaccines, FDA has determined that such conditions are necessary to protect the public health. Accordingly, the Letter of Authorization for each of the Authorized COVID-19 Vaccines contains conditions related to printed matter, advertising, and promotion.¹⁴² Given the current public health emergency, FDA does not see a need to expend the resources

¹³⁹ Concerns about potential State vaccine requirements are better directed to the States. FDA does not mandate use of vaccines.

¹⁴⁰ EUA Guidance at 26.

¹⁴¹ Id. at 27.

¹⁴² FDA, Pfizer-BioNTech COVID-19 Vaccine Letter of Authorization (Aug. 12, 2021), <https://www.fda.gov/media/150386/download>; FDA, Moderna COVID-19 Vaccine Letter of Authorization (Aug. 12, 2021), <https://www.fda.gov/media/144636/download>; FDA, Janssen COVID-19 Vaccine Letter of Authorization (June 10, 2021), <https://www.fda.gov/media/146303/download>.

necessary to develop and issue additional guidance on this topic. Thus, because FDA has already issued guidance addressing advertising and promotion of EUA products, and because FDA has established conditions related to printed matter, advertising, and promotion for all of the Authorized COVID-19 Vaccines, FDA denies Petitioner's request to issue additional guidance on this issue.

c. Conclusion

FDA has considered Petitioner's requests as they relate to the Authorized COVID-19 Vaccines and the approved COVID-19 Vaccine. For the reasons given in this letter, FDA denies the requests in Petitioner's citizen petition. Therefore, we deny the Petition in its entirety.

Sincerely,

A handwritten signature in black ink that reads "Peter Marks". The signature is written in a cursive, slightly stylized font.

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)¹⁴³ 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.

¹⁴³ Also referred to as Pharmaceutical Quality/CMC.