TESTIMONY

OF

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BEFORE THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS
UNITED STATES SENATE

"AN UPDATE FROM FEDERAL OFFICIALS ON EFFORTS TO COMBAT COVID-19"

MAY 11, 2021

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Chair Murray, Ranking Member Burr, distinguished members of the Committee, I am Dr. Peter Marks, Director of the Center for Biologics Evaluation and Research (CBER) at the U.S. Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to testify before you today to describe FDA's coronavirus disease 2019 (COVID-19) response efforts. All of our efforts are in close coordination and collaboration with our partners, both within the Department of Health and Human Services (HHS) and across the Federal government, to help ensure the development, authorization, licensure, and availability of critical, safe, and effective medical products to address the COVID-19 public health emergency.

While my testimony will focus on FDA's work regarding COVID-19 vaccines, I want to note at the outset that this is in the context of the breadth of work FDA is doing across the Agency to address this pandemic, including our efforts on diagnostics and therapeutics.

With the urgency called for during this pandemic, FDA, through our transparent scientific review process, has issued Emergency Use Authorization (EUA) for three COVID-19 vaccines. In doing so, we have relied upon the Agency's rigorous standards for safety, effectiveness, and manufacturing quality. Vaccine development is a highly de-risked process that generally proceeds sequentially through the various stages of clinical development, and manufacturing scale-up only takes place when the data support the safety and effectiveness of a vaccine and is on track for regulatory approval. These vaccines were developed without cutting corners or sacrificing our standards. Intensive interactions between FDA and manufacturers minimized the time between different studies in the clinical development process; allowed seamless movement throughout the different phases of clinical trials; and simultaneously proceeded with manufacturing scale-up before it was clear whether the safety and effectiveness data for a vaccine would support emergency use authorization.

For the three vaccines authorized to date, our EUA process not only included a thorough evaluation of the data by the Agency's career staff, but also included input from independent scientific and public health experts through our public advisory committee process. Throughout this process, FDA took additional steps to facilitate transparency, such as posting sponsor and FDA briefing documents and key decisional memoranda.

The three authorizations make available COVID-19 vaccines in the United States that have shown clear and compelling effectiveness in large, well-designed phase 3 trials and that meet rigorous standards for safety and effectiveness to support emergency use authorization. Vaccines are helping us in the fight against this pandemic, which has claimed almost 600,000 lives here in the United States alone. All the COVID-19 vaccines that FDA has authorized for emergency use have far surpassed being at least 50 percent more effective than placebo in preventing COVID-19, which was recommended in our June 2020 guidance document, *Development and Licensure of Vaccines to Prevent COVID-19*.[1] A vaccine with at least 50 percent efficacy would have a significant impact on disease, both at the individual and societal level.

[1] *https://www.fda.gov/media/139638/download*

As part of our continued efforts to be transparent and educate the public, we have a wealth of information on our website about the authorized COVID-19 vaccines. The information includes fact sheets for healthcare providers (vaccination providers) and vaccine recipients with important information such as dosing instructions; information about the benefits and risks of each authorized vaccine; and topical Questions and Answers developed by FDA for each authorized vaccine.[2]

It is also important to highlight that, as part of each EUA, we are requiring the manufacturers and vaccination providers to report serious adverse events, cases of Multisystem Inflammatory Syndrome (MIS), and cases of COVID-19 that result in hospitalization or death to the Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety surveillance program jointly run by FDA and the Centers for Disease Control and Prevention (CDC).

At this time, data are not available to make a determination about how long these authorized vaccines will provide protection, nor are we certain that the vaccines prevent transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from person to person. Additionally, although we do not yet know the full range of SARS-CoV-2 variants that each of the authorized vaccines will protect against, there is evidence that the current vaccines protect against disease caused by variants circulating in the United States.

Finally, manufacturers whose COVID-19 vaccines have been authorized for emergency use are expected to continue their clinical trials in order to obtain additional safety and effectiveness information and pursue licensure (approval) through the submission of a Biologics License Application (BLA).

FDA's role working with COVID-19 vaccine manufacturers

FDA plays a critical role in the development and authorization or licensure of vaccines, spanning the entire product lifecycle. The Agency provides scientific and regulatory advice to industry, researchers, and other stakeholders across the vaccine development spectrum. Interactions with product developers begin long before any formal regulatory submission is made and continue throughout development under FDA's investigational new drug application process. FDA is committed to working with all manufacturers developing products to prevent or treat COVID-19 and has had numerous interactions with COVID-19 vaccine manufacturers developing these vaccines and seeking emergency use authorization.

FDA makes use of all available regulatory tools and expedited programs, as appropriate, to help advance products critical for public health, including vaccines, from early product development to when a product application is submitted to FDA for our evaluation of safety and effectiveness to support authorization or approval.

[2] *https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-frequently-asked-questions*

Following approval of a BLA or issuance of an EUA request, the Agency uses real-world data to monitor the safety and effectiveness of vaccines through both passive and active post-market surveillance. Passive surveillance involves the submission of adverse event reports by patients, providers, and manufacturers to FDA through the Vaccine Adverse Event Reporting System (or VAERS). The Agency also performs active post-market surveillance of safety and effectiveness of vaccines through various databases, including an FDA partnership with the Center for Medicare & Medicaid Services (CMS) to use Medicare data and use of the FDA's of BEST (Biologics Evaluation and Safety) system.

FDA works with manufacturers of approved or authorized products to help ensure continued supply and availability of critical medical products. The Agency does this by promptly reviewing proposed technical or manufacturing changes and monitoring the continued quality of these products.

FDA is committed to providing timely scientific and regulatory advice to support rapid COVID-19 response efforts. To assist manufacturers with the development of COVID-19 vaccines, provide scientific and regulatory advice, and outline FDA's expectations, the Agency issued specific COVID-19 vaccine guidances. In June 2020, FDA issued guidance titled *Development and Licensure of Vaccines to Prevent COVID-19*. In October 2020, FDA issued guidance titled *Emergency Use Authorization for Vaccines to Prevent COVID-19* and updated it in February 2021.[3]

During the COVID-19 public health emergency, FDA is utilizing all available tools and sources of information to support regulatory decisions on applications or EUA requests that include manufacturing sites where FDA's ability to inspect facilities is impacted due to COVID-19. During this interim period, we are using additional tools, where available, to determine the need for an on-site inspection and to support the application assessment, such as reviewing a firm's previous compliance history, and requesting records in advance of or in lieu of on-site inspections or voluntarily from facilities and sites. Following notice by a sponsor of intent to submit an EUA request, FDA will continue to work with the sponsor regarding resolution of any necessary manufacturing site issues resulting from a site visit or other information submitted. FDA will assess current good manufacturing practices (CGMP) or CGMP compliance for each manufacturing site using all available tools and information.

The EUA Process for COVID-19 Vaccines

A determination by the previous HHS Secretary issued on February 4, 2020, declared that there is a public health emergency that has significant potential to affect national security or the health and security of U.S. citizens living abroad. Declarations were issued stating that circumstances exist justifying the authorization of emergency use of unapproved products. These declarations permit FDA to issue EUAs to allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent COVID-19 when there are no adequate, approved, and available alternatives.

[3] *https://www.fda.gov/media/142749/download*

The issuance of an EUA is different than an FDA approval (licensure) of a vaccine, in that a vaccine available under an EUA is not approved. In determining whether to issue an EUA for a vaccine, FDA evaluates the available evidence to determine whether the product may be effective, and assesses any known or potential risks and any known or potential benefits. If there is evidence that convinces us that the vaccine may be effective and the benefit-risk assessment is favorable, it may be made available during the public health emergency. Once a manufacturer submits an EUA request for a COVID-19 vaccine to FDA, the Agency 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 FDA.

The EUA requires fact sheets that provide important information, including dosing instructions and information about the benefits and risks of the COVID-19 vaccines, be made available to vaccination providers and vaccine recipients.

Each of the manufacturers of FDA-authorized COVID-19 vaccines submitted a pharmacovigilance plan to FDA describing their commitment to monitor the safety of their vaccines. The pharmacovigilance plans include plans to complete longer-term safety follow-up for participants enrolled in ongoing clinical trials. The pharmacovigilance plans also include other activities aimed at monitoring the safety profile of the COVID-19 vaccines and ensuring that any safety concerns are identified and evaluated in a timely manner. FDA also expects manufacturers whose COVID-19 vaccines are authorized under an EUA to continue their clinical trials to obtain additional safety and effectiveness information and pursue approval (licensure).

FDA, CDC, Centers for Medicare & Medicaid Services (CMS), Veteran's Health Administration and Department of Defense are conducting post-authorization safety and effectiveness monitoring in their surveillance systems including VAERS, CMS Medicare data, FDA BEST, the CDC Vaccine Safety Datalink and others.

Specific updates about each of the authorized vaccines are provided below.

PFIZER COVID-19 VACCINE

As Pfizer announced, FDA received the company's request to amend its emergency use authorization (EUA) to expand the authorized age range for its COVID-19 vaccine to include individuals 12 through 15 years of age. Currently, the vaccine is authorized for emergency use to prevent COVID-19 in individuals ages 16 and older. While the Agency cannot predict how long its evaluation of the data and information will take, we will review the request as expeditiously as possible using a thorough and science-based approach. Based on an initial evaluation of the information submitted, at this time the Agency does not plan to hold a meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) pertaining to this request to amend the EUA for the Pfizer-BioNTech COVID-19 Vaccine. The original EUA request was discussed at a VRBPAC meeting in December 2020. The VRBPAC voted in favor of the determination that based on the totality of scientific evidence available, the benefits of the Pfizer-BioNTech COVID-19 Vaccine outweigh its risks for use in individuals 16 years of age and older. After considering all the evidence, including the VRBPAC's advice, FDA issued an

EUA for the Pfizer vaccine. As with all FDA-authorized COVID-19 vaccines, we are committed to transparency with this EUA review process.

MODERNA COVID-19 VACCINE

On April 1, 2021, FDA announced two revisions regarding the number of doses per vial available for the Moderna COVID-19 Vaccine. The first revision clarifies the number of doses per vial for the vials that are available, in that the maximum number of extractable doses is 11, with a range of 10 – 11 doses. The second revision authorizes the availability of an additional multi-dose vial in which each vial contains a maximum of 15 doses, with a range of 13 – 15 doses that can potentially be extracted. The type of syringes and needles used to extract each dose affect the number of doses that can be extracted from the vials.

Both of these revisions positively impact the supply of Moderna COVID-19 Vaccine, which will help provide more vaccine doses to communities and permit more people to be vaccinated. Ultimately, more vaccinations administered in a timely manner in the United States and around the world should help bring an end to the pandemic more rapidly.

Depending on the type of syringes and needles used to extract each dose, there may not be sufficient volume to extract more than 10 doses from the vial containing a maximum of 11 doses or more than 13 doses from the vial containing a maximum of 15 doses.

To support these changes to the EUA, FDA evaluated data showing the number of doses that could be extracted from the vials and on the fill volumes for both vials that were submitted by ModernaTX, Inc. The Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) and Prescribing Information[4] have been revised to reflect the new information and are intended to help frontline workers administering COVID-19 vaccines understand the number of doses that can potentially be extracted per vial.

JANSSEN (JOHNSON & JOHNSON) COVID-19 VACCINE

As part of our regulatory processes for reviewing all manufacturing facilities, FDA recently completed an inspection of Emergent BioSolutions, a proposed manufacturing facility for the Janssen COVID-19 Vaccine. As Johnson & Johnson announced last month, FDA has not authorized this facility to manufacture or distribute any of the Janssen COVID-19 Vaccine or components and, to date, no COVID-19 vaccine manufactured at this plant has been distributed for use in the U.S.

FDA's inspections are thorough, and these assessments review the quality of manufacturing procedures, including records, staff training, facility operations, drug production and testing, and the systems in place to ensure product quality. At the close of the inspection of Emergent BioSolutions, FDA investigators cited a number of observations concerning whether the

[4] *https://www.fda.gov/media/144637/download*

facility's practices met our regulatory requirements and standards. These observations are outlined in an inspection closeout report, also known as an "FDA Form 483."[5]

Typically, firms respond to the observations cited on an FDA Form 483, and the Agency then works with a company to help identify a path forward to remedy the issues.

Indeed, it is often in the public's best interest that FDA work with firms to quickly resolve inspectional observations to ensure that the public has access to medical products that meet the Agency's high standards for quality, safety, and effectiveness.

In the case of Emergent BioSolutions, we are working with the company to address the conditions identified. At the Agency's request, Emergent BioSolutions has agreed to pause new production while it works with FDA to resolve potential quality issues. For the vaccines already manufactured, the products will undergo additional testing and will be thoroughly evaluated to ensure their quality before any potential distribution. We will not allow the release of any product until we are confident that it meets our expectations for quality.

We have notified various health authorities regarding the findings we observed at the Emergent facility and are providing additional information as requested. FDA will continue to work closely with its international partners, as it has throughout the pandemic. Additionally, moving forward, the Agency is considering how best to further evaluate manufacturing quality during this and any future public health emergency.

These manufacturing actions are unrelated to an ongoing evaluation by FDA and CDC of clinical reports of blood clots along with low levels of platelets that have occurred in some people after receiving the Janssen COVID-19 Vaccine, described further below.

We are committed to ensuring that the COVID-19 vaccines given to the people of this nation have met the Agency's high standards for quality, safety, and effectiveness. We know that every time a person, including members of our own families, receives a COVID-19 vaccine, they are putting their trust in us. We are committed to maintaining that trust.

COVID-19 VACCINE SAFETY SURVEILLANCE

On April 13, 2021, FDA and CDC issued a joint statement, announcing that, out of more than 6.8 million doses administered as of that date, six reports of a rare and severe type of blood clot combined with low blood platelet levels occurring in people after receiving the Janssen COVID-19 Vaccine had been reported to VAERS. In these cases, a type of blood clot called cerebral venous sinus thrombosis (CVST) was seen in combination with low levels of blood platelets (thrombocytopenia). All six cases occurred among women between the ages of 18 and 48, and symptoms occurred 6 to 13 days after vaccination. Treatment of this specific type of blood clot is different from the treatment that might typically be administered. Usually, an anticoagulant

[5] *https://www.fda.gov/media/147762/download*

drug called heparin is used to treat blood clots. In this circumstance, administration of heparin may be dangerous, and alternative treatments need to be given.

Out of an abundance of caution, FDA and CDC recommended a pause in the use of the Janssen COVID-19 Vaccine while we investigated reports of these serious adverse events. This was important, in part, to help ensure that health care providers were made aware of the potential occurrence of these adverse events and could plan for proper recognition and clinical management due to the unique treatment required for thrombosis with thrombocytopenia syndrome.

FDA and CDC have reviewed all of the available data, and CDC's Advisory Committee on Immunization Practices (ACIP) held emergency meetings to discuss the data on April 14 and April 23, 2021. Those data, plus the deliberations and recommendations of the ACIP, informed our assessment that the known and potential benefits of Janssen COVID-19 Vaccine outweigh its known and potential risks in individuals 18 years of age and older. We concluded that, at this time, the available data suggest that the chance of this serious adverse event occurring is very low. Thus, on April 23, 2021, FDA and CDC determined that the recommended pause regarding the use of the Janssen COVID-19 Vaccine in the U.S. should be lifted and use of the vaccine should resume. However, investigation into the level of potential excess risk due to COVID-19 vaccination is ongoing.

The Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) has been updated to include a Warning pertaining to the risk of thrombosis with thrombocytopenia.[6] The Fact Sheet for Recipients and Caregivers has also been updated to include information about these serious adverse events.

FDA and CDC will continue to closely monitor the safety of these vaccines. We will continue to closely monitor the safety of the Janssen COVID-19 Vaccine.

The pause in the use of this vaccine was an example of our extensive safety monitoring system working as it is designed to work—identifying even this small number of cases.

As of May 4, 2021, a total of 23 cases of thrombosis with thrombocytopenia following post-authorization use of Janssen COVID-19 Vaccine were confirmed, involving cerebral venous sinuses and other sites in the body. These cases have been associated with three deaths. FDA anticipates these numbers will change over time as additional cases are reported and investigated.

FDA continues to inform the public of these cases and has noted that a causal relationship with Janssen COVID-19 Vaccine is plausible for thrombosis with thrombocytopenia syndrome. The teams at FDA and CDC also conducted extensive outreach to providers and clinicians to ensure they were made aware of the potential for these adverse events. The outreach also provided information so that they could properly clinically manage and recognize these events due to the unique treatment required for these blood clots and low platelets, also known as thrombosis-

[6] *https://www.fda.gov/media/146304/download*

thrombocytopenia syndrome (TTS). Specific risk factors for thrombosis with thrombocytopenia after vaccination continue to be investigated.

As noted earlier, CBER is monitoring the safety of *all* authorized COVID-19 vaccines through both passive and active safety surveillance systems. CBER is doing so in collaboration with CDC, CMS, the Department of Veterans Affairs, and other academic and large non-government healthcare data systems. In addition, CBER participates actively in ongoing international pharmacovigilance efforts, including those organized by the International Coalition of Medicines Regulatory Authorities and the World Health Organization. These efforts are in addition to the pharmacovigilance efforts being undertaken by the individual COVID-19 vaccine manufacturers for authorized vaccines. A coordinated and overlapping approach using state-of-the-art technologies has been implemented.

CONCLUSION

The process FDA uses to evaluate the safety and effectiveness of medical products is respected worldwide and commonly referred to as the "gold standard." Because of a well-established history, the Agency's review processes are globally recognized as the most rigorous.

Having three vaccines authorized to date that meet FDA's expectations for safety and effectiveness only one year after the declaration of the COVID-19 pandemic is a tremendous achievement and a testament to the dedication of developers and FDA's career scientists and physicians, many of whom have been working tirelessly to conduct comprehensive and rigorous evaluations of the data submitted for vaccines to prevent COVID-19. We are highly engaged in ensuring that all COVID-19 vaccines meet the high quality that Americans expect and deserve and are also actively engaged in ensuring the safety of these vaccines following deployment. The Agency is very proud of these efforts, and we hope that the vaccines will help bring this pandemic to an end.