TESTIMONY

OF

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"EXAMINING OUR COVID-19 RESPONSE: AN UPDATE FROM FEDERAL OFFICIALS"

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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 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 coronavirus disease 2019 (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 provided 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 it is very clear that the vaccine is safe and effective and is on track for regulatory approval. These vaccines were developed without cutting corners or sacrificing our standards. Intensive interactions between FDA and manufacturers eliminated the time between different studies in the clinical development process; allowed seamless movement between the different phases of clinical trials; and simultaneously proceeded with manufacturing scale-up before it was clear whether the vaccine would be shown to be safe and effective. 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 efficacy in large, well-designed phase 3 trials and that meet rigorous standards for safety and effectiveness. Vaccines will help us in the fight against this pandemic, which has claimed over half a million lives here in the United States alone. All the COVID-19 vaccines that FDA has authorized for emergency use have surpassed the standard of being at least 50 percent more effective than placebo in preventing COVID-19, which was the standard 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.

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

It is also important to highlight that, as part of the 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 the 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.

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).

[1] *https://www.fda.gov/media/139638/download*
[2] *https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-frequently-asked-questions*

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 studying these products 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, from product development to when a product application is submitted to FDA for our evaluation of safety and effectiveness to support approval.

Following approval of a BLA or authorization of an EUA request, the Agency uses real-world data to monitor the safety 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. The Agency also performs active post-market surveillance of vaccines through various databases, including FDA's Sentinel 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. For example, CBER recently reviewed data submitted by Pfizer to FDA to allow undiluted frozen vials of the Pfizer-BioNTech COVID-19 vaccine to be transported and stored at conventional temperatures commonly found in pharmaceutical freezers for up to two weeks. This will help ease the burden of procuring ultra-low cold storage equipment for vaccination sites and should help get vaccine to more sites.

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 recommendations, 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 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 permitted 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.

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

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

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 is 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).

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

PFIZER COVID-19 VACCINE

On December 11, 2020, FDA issued the first EUA for a vaccine for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. The EUA allows the Pfizer-BioNTech COVID-19 Vaccine to be distributed in the United States

The Pfizer-BioNTech COVID-19 Vaccine contains messenger RNA (mRNA), which is genetic material. The vaccine contains a small piece of the SARS-CoV-2 virus' mRNA that instructs cells in the body to make the virus' distinctive "spike" protein. When a person

receives this vaccine, their body produces copies of the spike protein, which does not cause disease, but triggers the immune system to produce an immune response against SARS-CoV-2.

FDA Evaluation of Available Safety Data

The Pfizer BioNTech COVID-19 Vaccine is administered as a series of two doses, three weeks apart. The available safety data to support the EUA include 37,586 participants enrolled in an ongoing randomized, placebo-controlled international study, the majority of whom are U.S. participants. These participants, 18,801 of whom received the vaccine and 18,785 of whom received saline placebo, were followed for a median of two months after receiving the second dose. The most commonly reported side effects, which typically lasted several days, were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, and fever. Of note, more people experienced these side effects after the second dose than after the first dose, so it is important for vaccination providers and recipients to expect that there may be some side effects after either dose, but more after the second dose.

FDA Evaluation of Available Effectiveness Data

The effectiveness data to support the Pfizer BioNTech EUA include an analysis of 36,523 participants in the ongoing randomized, placebo-controlled international study, the majority of whom are U.S. participants, who did not have evidence of SARS-CoV-2 infection through seven days after the second dose. Among these participants, 18,198 received the vaccine and 18,325 received placebo. The vaccine was 95 percent effective in preventing COVID-19 disease among these clinical trial participants with eight COVID-19 cases in the vaccine group and 162 in the placebo group. Of these 170 COVID-19 cases, one in the vaccine group and three in the placebo group were classified as severe.

MODERNA COVID-19 VACCINE

On December 18, 2020, FDA issued an EUA for the second vaccine for the prevention of COVID-19 caused by SARS-CoV-2. The EUA allows the Moderna COVID-19 Vaccine to be distributed in the U.S for use in individuals 18 years of age and older.

Like the Pfizer-BioNTech COVID-19 Vaccine, the Moderna COVID-19 Vaccine contains a small piece of the SARS-CoV-2 virus' mRNA that instructs cells in the body to make the virus' distinctive "spike" protein. After a person receives this vaccine, their body produces copies of the spike protein, which does not cause disease, but triggers the immune system to produce an immune response against SARS-CoV-2.

FDA Evaluation of Available Safety Data

The Moderna COVID-19 Vaccine is administered as a series of two doses, one month apart. The available safety data to support the EUA include an analysis of 30,351 participants enrolled in an ongoing randomized, placebo-controlled study conducted in the U.S. These participants, 15,185 of whom received the vaccine and 15,166 of whom received saline placebo, were followed for a median of more than two months after receiving the second dose. The most commonly reported side effects, which typically lasted several days, were pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, swollen lymph nodes in the same arm as the injection, nausea and vomiting, and fever. Of note, more people experienced these side effects after the second dose than after the first dose, so it is important for vaccination providers and recipients to expect that there may be some side effects after either dose, but more after the second dose.

FDA Evaluation of Available Effectiveness Data

The effectiveness data to support the Moderna COVID-19 EUA include an analysis of 28,207 participants in the ongoing randomized, placebo-controlled U.S. study who did not have evidence of SARS-CoV-2 infection prior to the first dose of vaccine. Among these participants, 14,134 received the vaccine and 14,073 received placebo. The vaccine was 94.1 percent effective in preventing COVID-19 disease among these clinical trial participants with 11 cases of COVID-19 in the vaccine group and 185 in the placebo group. At the time of the analysis of these 196 COVID-19 cases, none in the vaccine group and 30 in the placebo group were classified as severe. After the analysis of these 196 cases was completed, one severe case in the vaccine group was identified and was awaiting confirmation at the time the EUA was issued.

JANSSEN (JOHNSON & JOHNSON) COVID-19 VACCINE

On February 27, 2021, FDA issued an EUA for the third vaccine for the prevention of COVID-19 caused by SARS-CoV-2. The EUA allows the Janssen COVID-19 Vaccine to be distributed in the United States for use in individuals 18 years of age and older.

The Janssen COVID-19 Vaccine is manufactured using a specific type of virus called adenovirus type 26 (Ad26). The vaccine uses Ad26 to deliver a piece of the DNA, or genetic material, that is used to make the distinctive "spike" protein of the SARS-CoV-2 virus. While adenoviruses are a group of viruses that are relatively common, Ad26, which can cause cold symptoms and pink eye, has been modified for the vaccine so that it cannot replicate in the human body or cause illness. After a person receives this vaccine, the body can temporarily make the spike protein, which does not cause disease, but triggers the immune system to produce an immune response against SARS-CoV-2.

FDA Evaluation of Available Safety Data

The Janssen COVID-19 Vaccine is administered as a single dose. The available safety data to support the EUA include an analysis of 43,783 participants enrolled in an ongoing randomized, placebo-controlled study being conducted in South Africa, certain countries in South America, Mexico, and the United States. The participants, 21,895 of whom received the vaccine and 21,888 of whom received saline placebo, were followed for a median of eight weeks after vaccination. The most commonly reported side effects were pain at the injection site, headache, fatigue, muscle aches, and nausea. Most of these side effects were mild to moderate in severity and lasted one to two days.

FDA Evaluation of Available Effectiveness Data

The effectiveness data to support the Janssen EUA include an analysis of 39,321 participants in the ongoing randomized, placebo-controlled study being conducted in South Africa, certain countries in South America, Mexico, and the United States who did not have evidence of SARS-CoV-2 infection prior to receiving the vaccine. Among these participants, 19,630 received the vaccine and 19,691 received saline placebo. Overall, the vaccine was

approximately 67 percent effective in preventing moderate to severe/critical COVID-19 occurring at least 14 days after vaccination and 66 percent effective in preventing moderate to severe/critical COVID-19 occurring at least 28 days after vaccination.

Additionally, the vaccine was approximately 77 percent effective in preventing severe/critical COVID-19 occurring at least 14 days after vaccination and 85 percent effective in preventing severe/critical COVID-19 occurring at least 28 days after vaccination.

There were 116 cases of COVID-19 in the vaccine group that occurred at least 14 days after vaccination, and 348 cases of COVID-19 in the placebo group during this time period. There were 66 cases of COVID-19 in the vaccine group that occurred at least 28 days after vaccination and 193 cases of COVID-19 in the placebo group during this time period. Starting 14 days after vaccination, there were 14 severe/critical cases in the vaccinated group versus 60 in the placebo group, and starting 28 days after vaccination, there were five severe/critical in the vaccine group versus 34 cases in the placebo group. In this trial, no individuals receiving the vaccine required hospitalization or died starting 28 days after the vaccine compared to 16 individuals receiving placebo.

COVID-19 VACCINE SAFETY SURVEILLANCE

CBER is monitoring the safety of authorized COVID-19 vaccines through both passive and active safety surveillance systems. CBER is doing so in collaboration with CDC, the Center for Medicare & Medicaid Services (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 manufacturers for authorized vaccines. A coordinated and overlapping approach using state-of-the-art technologies has been implemented.

Passive Surveillance

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 the Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety monitoring system co-managed by FDA and CDC. In the current pandemic, these reports are being used in conjunction with other vaccine safety systems to monitor the occurrence of certain adverse events including serious adverse events, as providers of COVID-19 vaccines are required to report these to VAERS. FDA efforts complement those of the v-safe text-based monitoring system for adverse events that CDC has implemented. An example of the work done with passive safety surveillance during the current pandemic has been the evaluation of severe allergic reactions following vaccination with the authorized mRNA-based COVID-19 vaccines. Through this work, we have come to understand that these reactions are quite rare, happening in fewer than five in one million vaccine doses administered.

Active Surveillance

Active surveillance involves proactively obtaining and rapidly analyzing information occurring in millions of individuals 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, which is part of the Sentinel initiative, 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 America, the Observational Health Data Sciences and Informatics, OneFlorida, University of California, and several others.

Using BEST, CBER plans to monitor about 15 adverse events that have been identified 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.

Collaboration with CMS

CBER 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. Because it was already in place, having demonstrated its use for the evaluation of influenza vaccine safety and efficacy, this system was immediately put into use for COVID-19 vaccine surveillance to monitor for adverse events.

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.

In summary, in collaboration and coordination with several different partners, CBER has assembled passive and active surveillance systems that can detect and refine safety findings with the recently 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, including against emerging variants.

NEXT STEPS

The emergence of the virus variants raises new concerns about the performance of these authorized vaccines, as well as therapeutics and diagnostics that FDA has authorized for COVID-19. In February 2021, FDA issued two new guidances and an update to its vaccine EUA guidance to address the emergence of SARS-CoV-2 variants of concern.[4] By issuing these guidances, we want the American public to know that we are using every tool in our medical toolbox to fight this pandemic, including pivoting as the virus adapts. These guidances will help manufacturers to develop medical products to provide health care providers with the best available diagnostics, therapeutics, and vaccines to fight this virus – even as variants emerge. We remain committed to getting these life-saving products to the frontlines.

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 and accurate.

Having three vaccines authorized that meet the FDA's expectations for safety and effectiveness only one year after the declaration of the pandemic is a tremendous

[4] *https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders*

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. The Agency is very proud of these efforts, and we hope that the vaccines will help bring this pandemic to an end.